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Ambient Water Quality Criteria for Chlorinated Phenols

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Chlorinated Phenols. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR
CHLORINATED PHENOLS

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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CRITERIA DOCUMENT

CHLORINATED PHENOLS

CRITERIA

Aquatic Life

The available freshwater data for chlorinated phenols indicate that toxicity generally increases with increasing chlorination, and that acute toxicity occurs at concentrations as low as 30 µg/l for 4-chloro-3-methylphenol to greater than 500,000 µg/l for other compounds. Chronic toxicity occurs at concentrations as low as 970 µg/l for 2,4,6-trichlorophenol. Acute and chronic toxicity would occur at lower concentrations among species that are more sensitive than those tested.

The available saltwater data for chlorinated phenols indicate that toxicity generally increases with increasing chlorination and that acute toxicity occurs at concentrations as low as 440 µg/l for 2,3,5,6-tetrachlorophenol and 29,700 µg/l for 4-chlorophenol. Acute toxicity would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of chlorinated phenols to sensitive saltwater aquatic life.

Human Health

Sufficient data are not available for 3-chlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.1 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 4-chlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.1 μg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 2,3-dichlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.04 μg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 2,5-dichlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.5 μg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 2,6-dichlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.2 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 3,4-dichlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.3 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

For comparison purposes, two approaches were used to derive criterion levels for 2,4,5-trichlorophenol. Based on available toxicity data, for the protection of public health, the derived level is 2.6 mg/l. Using available organoleptic data, for controlling undesirable taste and odor quality of ambient water, the estimated level is 1.0 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of 2,4,6-trichlorophenol through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 12 µg/l, 1.2 µg/l, and 0.12 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 36 µg/l, 3.6 µg/l, and 0.36 µg/l, respectively. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 2 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 2,3,4,6-tetrachlorophenol to derive a level which would protect against the potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 1 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 2-methyl-4-chlorophenol to derive a criterion level which would protect against any potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 1,800 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 3-methyl-4-chlorophenol to derive a criterion level which would protect against any potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 3,000 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

Sufficient data are not available for 3-methyl-6-chlorophenol to derive a criterion level which would protect against any potential toxicity of this compound. Using available organoleptic data, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 20 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criterion have limitations and have no demonstrated relationship to potential adverse human health effects.

INTRODUCTION

The chlorinated phenols represent a group of commercially produced, substituted phenols and cresols referred to as chlorophenols and chlorocresols. Chlorinated phenols are used as intermediates in the synthesis of dyes, pigments, phenolic resins, pesticides, and herbicides. Certain chlorophenols also are used directly as flea repellents, fungicides, wood preservatives, mold inhibitors, antiseptics, disinfectants, and antigumming agents for gasoline. (The compounds 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol are discussed in separate criteria documents.)

The chlorinated phenols represent a group of substituted phenols and cresols prepared by direct chlorination or the hydrolysis of the higher chlorinated derivatives of benzene. Purified chlorinated phenols exist as colorless crystalline solids, with the exception of 2-chlorophenol which is a clear liquid, while the technical grades may be light tan or slightly pink due to impurities (Bennett, 1962; Kirk and Othmer, 1964; Heilbron, et al. 1975; Sax, 1975; Weast, 1974; Windholz, 1976; Hawley, 1975). As a group, the chlorophenols are characterized by an odor which has been described as unpleasant, medicinal, pungent, phenolic, strong, or persistent (Kirk and Othmer, 1964; Sax, 1975; Lange, 1952).

A summary of the various pertinent physical properties is presented in Table 1. In general, the volatility of the compounds decreases and the melting and boiling points increase as the number of substituted chlorine atoms increases. The solubility of the chlorophenols and chlorocresols, with the exception of 2,4,6-trichloro-m-cresol, range from soluble to very soluble in relatively

TABLE 1

Physical Properties of Chlorinated Phenols

Compound	MW	pK	MP (deg. C)	BP (deg. C)	Density	Water Sol. (g/100g)*	Vapor Pressure (mm Hg/ deg. C)
Chlorophenols							
3-	128.56	9.08	33.	214	1.2680	0.26	1/12.1
4-	128.56	9.42	43.2	217	1.2651	2.71	
2,3-di-	163	7.70	57.	---	---	---	
2,5-di-	163	7.51	59	211	---	sl.	
2,6-di-	163	6.79	67	219	---	---	1/59.5
3,4-di-	163	8.59	68	253	---	sl.	
3,5-di-	163	8.19	68	233	---	s.	
2,3,4-tri	197.5	---	83.5	Sublimes	---	---	
2,3,5-tri-	197.5	---	62	248.5	---	s.	
2,3,6-tri-	197.5	---	58	272	1.4901	sl.	
2,4,5-tri	197.5	7.0	68	Sublimes	---	0.2	1/72.0
2,4,6-tri-	197.5	6.1	69.5	246	---	0.1	1/76.5
2,3,4,5-tetra-	232	---	116	Sublimes	1.6700	---	
2,3,5,6-tetra-	232	5.3	115	---	---	0.1	
Chloro-o-cresols							
3-	142.55	---	86	225	---	sl.	
4-	142.59	---	51	223	---	sl.	
5-	142.59	---	73	---	---	---	
6-	142.59	---	---	188.9	---	sl.	
4,5-di-	177.03	---	101	---	---	sl.	
4,6-di-	177.03	---	55	266.5	---	sl.	
3,4,5-di-	177.03	---	101	---	---	sl.	
3,4,6-di-	177.03	---	55	226	---	sl.	
3,4,6-tri-	211.5	---	62	---	---	---	
4,5,6-tri-	211.5	---	77	269	---	sl.	
3,4,5,6-tetra-	245.9	---	190	---	---	---	

TABLE 1 (Continued)

Compound	MW	pK	MP (deg. C)	BP (deg. C)	Density	Water Sol. (g/100g)	Vapor Pressure (mm Hg/ deg. C)
Chloro-m-cresols							
2-	142.59	---	55	196	---	sl.	
4-	142.59	---	43	220	---	0.38	
6-	142.59	---	45	196	---	s.	
2,4-di-	177.03	---	27	241	---	---	
2,6-di-	177.03	---	58	235	---	---	
4,6-di-	177.03	---	72	235	---	---	
2,4,6-tri-	211.48	---	45	265	---	sl.	
2,4,5,6-tetra-	245.92	---	189	---	---	s.	
Chloro-p-cresols							
2-	142.59	---	---	195.6	---	sl.	
3-	142.59	---	55	228	---	s.	
2,6-di-	177.03	---	39	138	---	sl.	
2,3,5,6-tetra-	245.42	---	190	---	---	---	

*sl = slightly soluble; s = soluble.

References:
1. Bennett, 1962
2. Kirk and Othmer, 1964
3. Heilbron, et al. 1975
4. Weast, 1978
5. Sax, 1975
6. Weast, 1974
7. Windholz, 1976
8. Pearce & Simkins, 1968

non-polar solvents such as benzene and petroleum ether. Although chlorophenols are considered weak acids, they are stronger acids than phenol and can be converted to the corresponding phenoxide salt by various bases including sodium carbonate. The dissociation constants (pKa) for the chlorinated phenols progressively decrease with increased substitution of chlorine atoms into the aromatic ring. Although the solubility of chlorinated phenols in aqueous solutions is relatively low, it increases markedly when the pH of the solution exceeds the specific pKa, since the more readily soluble phenoxide salt is formed. The phenoxide salts are also more soluble than the corresponding phenol in water at neutral pH.

A summary of the methods of synthesis and principal uses of the commercially most important chlorinated phenols is presented in Table 2. Since the hydroxyl group of the phenol molecule exerts a relatively strong ortho-para-directing influence over the electrophylic substitution of chlorine atoms, the compounds preferentially formed during the direct chlorination of phenol are 4-chlorophenol, 2-chlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol, 2,4,6-trichlorophenol, and 2,3,4,6-tetrachlorophenol. Other positional isomers may be synthesized by the hydrolysis of higher chlorobenzenes. Many of the chlorinated phenols have no commercial application presently due to their high cost of production, complex synthetic procedures, or lack of useful chemical, physical, or toxicological properties (Kirk and Othmer, 1964). These include 3-chlorophenol, 2,3-dichlorophenol, 2,5-dichlorophenol, 3,4-dichlorophenol, 3,5-dichlorophenol, 2,3,4-trichlorophenol, 2,3,5-trichlorophenol, 2,3,4,5-tetrachlorophenol, and 2,3,5,6-tetra-

TABLE 2

Summary of the Synthesis and Uses of Various Chlorinated Phenols

Chlorinated Phenol	Method of Synthesis	Principal Uses	References
4-chlorophenol (4-CP)	Direct chlorination of phenol	To produce 2,4-DCP, and a germicide 4-chlorophenol-o-cresol	Kirk & Othmer, 1964
2,4-dichlorophenol (2,4-DCP)	Direct chlorination of phenol	To produce herbicide 2,4-D, also a mothproofing cpd., an antiseptic and a miticide	U.S. EPA, 1973; Kirk & Othmer, 1964
2,4,5-trichlorophenol (2,4,5-TCP)	Hydrolysis of 1,2,4,5-tetrachlorobenzene	To produce defoliant 2,4,5-T and related products. Also used directly as a fungicide, antimildew and preservative agent, algicide, bactericide	U.S. EPA, 1973; Kirk & Othmer, 1964
2,4,6-trichlorophenol (2,4,6-TCP)	Direct chlorination of phenol	To produce 2,3,4,6-TCP and PCP. Used directly as germicide, bactericide, glue and wood preservative and antimildew treatment	U.S. EPA, 1973; Kirk & Othmer, 1964
2,3,4,6-tetrachlorophenol (2,3,4,6-TCP)	Direct chlorination of phenol or lower chlorophenols	Used directly as bactericide, fungicide, insecticide, wood and leather preservative	U.S. EPA, 1973; Kirk & Othmer, 1964
Pentachlorophenol (PCP)	Direct chlorination of phenol or lower phenols	Used directly as a wood preservative, herbicide, insecticide and moluscicide	Kirk & Othmer, 1964
4-chloro-o-cresol (4-c-o-c)	Direct chlorination of o-cresol	To produce the herbicide MCPA	U.S. EPA, 1973; Kirk & Othmer, 1964

chlorophenol. However, each of these compounds is produced to some extent as a by-product during the production of the commercially important chlorophenols. From a commercial standpoint, 4-chloro-o-cresol is the most important of the chlorinated cresols (Kirk and Othmer, 1964).

It is well known that the highly toxic polychlorinated dibenzo-p-dioxins may be formed during the chemical synthesis of some chlorophenols, and that the amount of contaminant formed is dependent upon the temperature and pressure control of the reaction (Fishbein, 1973; Milnes, 1971; Schulz, 1968; Higgenbotham, et al. 1968; Muelder and Shadoff, 1973). The toxicity of the dioxins varies with the position and number of substituted chlorined atoms and those containing chlorine in the 2,3 and 7 positions are particularly toxic (Burger, 1973). The 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is considered the most toxic of all the dioxins (Sparschu, et al. 1971).

TCDD is apparently formed during the synthesis of 2,4,5-trichlorophenol and before 1968 was reported to be present in the subsequent product 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) at levels up to 10 mg/kg (Kearney, et al. 1973; Fishbein, 1973). By 1971 TCDD levels in commercial 2,4,5-T were below 1 mg/kg (Greig, et al. 1973; Hussain, et al. 1972) and are currently reported to be below 0.099 mg/kg (Dow, 1977).

No TCDD was reported present in samples of commercial grade tetrachlorophenol although 28, 80, and 30 mg/kg of the hexachloro-, heptachloro-, and octachlorodibenzo-p-dioxins and 55, 100, and 25 mg/kg of the hexachloro-, heptachloro-, and octachlorodibenzofurans were present, respectively (Schwetz, et al. 1974a). No TCDD has been reported present in commercial pentachlorophenol products although hexa-, hepta-, and octochlorodibenzo-p-dioxins have been detected at concentrations of 4 to 27 mg/kg, 125 mg/kg, and 50 to 2,510 mg/kg, respectively (Johnson, et al. 1973; Jensen and Reuberg, 1973; Schwetz, et al. 1974b).

Evidence has accumulated that the various chlorophenols are formed as intermediate metabolites during the microbiological degradation of the herbicides 2,4-D and 2,4,5-T and pesticides Silvex®, Ronnel®, lindane, and benzene hexachloride (Kearney and Kaufman, 1972; Steenson and Walker, 1957; Fernley and Evans, 1959; Loos, et al. 1967; Aly and Faust, 1964; Crosby and Tutass, 1966; Watts and Stonherr, 1973; Crosby and Wong, 1973; Goto, et al 1972; Leng, 1976). In veiw of the information presented, it is clear that chlorinated phenols represent important compounds with regard to potential point source and non-point source water contamination.

Chlorophenols may be produced inadvertently by chlorination reactions which take place during the disinfection of waste water effluents or drinking water sources. Phenol has been reported to be highly reactive to chlorine in dilute aqueous solutions over a considerable pH range (Carlson and Caple, 1975; Middaugh and Davis, 1976). The formation of 2- and 4-chlorophenol and higher phenols has been reported under conditions similar to those employed during the disinfection of waste water effluents (Aly, 1968; Barnhart and Campbell, 1972) and the synthesis of 2-chlorophenol took place in one hour in aqueous solutions containing as little as 10 mg/l phenol and 20 mg/l chlorine (Barnhart and Campbell, 1972). Other studies have demonstrated the formation of up to 1.7 μg/l 2-chlorophenol during the chlorination of sewage effluents and cooling tower waters (Jolly, 1973; Jolly, et al. 1975).

Limited data are available on levels of chlorinated phenols present in industrial and municipal wastes, natural waters, drinking waters, or soils and sediments. 3-Chlorophenol, 4-chlorophenol, and 4-chloro-3-methylphenol (4-chloro-m-cresol) have been identified in chlorinated samples of both primary and secondary effluents and pentachlorophenol was found in domestic sewage treatment effluents (U.S. EPA, 1975). However, no quantitative data were reported. Examples of some findings are: the presence of 2,4-dichlorophenol in a local water intake system at a concentration of 6.6 μg/l has been noted. Pentachlorophenol concentrations of 4.3 μg/l (1 to 5 μg/l range) in some sewage effluent have been reported. In another case, a river used as a drinking water supply contained 0.10 to 0.70 μg/l pentachlorophenol with 40 percent of these levels retained in the finished drinking water. The presence of 10 to 18 mg/l pentachlorophenol was found in a study of a small stream near a wood preservation site with surface oil slicks containing 5,800 mg/l pentachlorophenol. In the same study, pentachlorophenol concentrations of 0.1 to 0.2 mg/l and 0.05 mg/l were found in samples taken 1/2 mile and 2 miles downstream, respectively.

It is generally accepted that chlorinated phenols will undergo photolysis in aqueous solutions as a result of ultraviolet irradiation and that photodegradation leads to the substitution of hydroxyl groups in place of the chlorine atoms with subsequent polymer formation. Studies by Grabowski (1961) and Joschek and Miller (1966) indicated that UV irradiation of 2-chlorophenol produced catechol and/or 2,2-dihydroxydiphenyl. Omura and Matsuura (1971) reported that UV irradiation (290 mμ) of 2-chlorophenol produced a complex mixture of products, including a large quantity of resinous material while the photolysis of 3-chlorophenol produced a high yield of resorcinol. Photolysis of 2,4-dichlorophenol in dilute aqueous solutions at a peak wavelength of 253.7 mμ was virtually complete within 2 to 40 minutes depending upon the pH (Aly and Faust, 1964).

Other studies have demonstrated the photodegradation of 2,4-dichlorophenol following five hours of daily solar irradiation for 10 days (Crosby and Tutass, 1966). They observed the formation of the intermediates 4-chlorocatechol and 1,2,4-benzenetriol. The principal product of degradation recovered was a dark brown residue tentatively identfied as a mixture of dechlorinated polyquinoids. Although it has been speculated that photolysis of chlorophenols may produce dibenzo-p-dioxins, no 2,3,7,8-tetrachlorodibenzo-p-dioxin was detected during the riboflavin-sensitized photooxidation of 2,4-dichlorophenol to tetrachlorinated diphenol ethers (Plimmer and Klingebiel, 1971). Pentachlorophenol (PCP) was shown to undergo photochemical degradation in aqueous solutions by ultraviolet irradiation and sunlight, with the formation of several chlorinated benzoquinones, 2,4,5,6-tetrachlororesorcinol, and chloranilic acid (Mitchell, 1961; Hamadmad, 1967). Wong and Crosby (1977) reported the degradation by sunlight or UV light of dilute solutions (100 mg/l) of pentachlorophenol to lower chlorophenols, tetrachlorodihydroxybenzenes, and non-aromatic fragments such as dichloromaleic acid. Subsequent irradiation of the tetrachlorodiols produced hydroxylated trichlorobenzoquinones, trichlorodiols, dichloromaleic acid, and non-aromatic compounds. The irradiation of dichloromaleic acid produced chloride ions and carbon dioxide.

Microbial degradation of chlorophenols has been reported by numerous investigators. Loos, et al. (1967) demonstrated the complete dechlorination and aromatic ring degradation of 2-chloro-, 4-chloro-, and 2,4-dichlorophenol by 2,4-D-grown cells of an *Arthrobacter* species isolated from silt loam. Evans, et al. (1971), reported the degradation of 2-chlorophenol by several *Pseudomonas* species isolated from soil. Nachtigall and Butler (1974), using a Warburg respirometric technique, observed the oxidation of all monochlorophenols, 2,4- and 2,6-dichlorophenol, and 2,4,6-trichlorophenol by *Pseudomonas* sp. obtained through enrichment of, and isolation from, activated sludge. Alexander and Aleem (1961) reported the resistance of 2,4,5-trichlorophenol to microbial decomposition by certain soil bacteria. They observed that compounds containing a meta-substituted chlorine atom (position 3 or 5) appeared to be more resistant to microbial degradation. Ingols, et al. (1966) reported the complete aromatic ring degradation of 2,4-dichloro- and 2,4,6-trichlorophenol within five days by microbial action of an acclimated sludge, while 2,5-dichlorophenol was degraded only 52 percent.

Conversely, the destruction of 2,3,4,6-tetrachlorophenol by numerous fungal species of *Aspergillus*, *Penicillium*, and *Scopu-*

lariopsis obtained from broiler house litter has been reported (Gee and Peel, 1974). In the same study, the tetrachlorophenol was completely metabolized by a mixed bacterial suspension also isolated from the litter. Although Ingols, et al. (1966), observed no alteration of sodium pentachlorophenol (NaPCP) by activated sludge microbes after four days of incubation, Watanabe (1973) reported the growth of an isolated species of Pseudomonas from PCP-perfused culture samples using PCP as the sole carbon source.

Organoleptic properties manifest themselves in two forms; the ability of a compound to impart taste or odor to water, and to cause tainting in fish flesh as a result of exposure to chlorophenol-contaminated water. The organoleptic properties of chlorophenols are well documented. The threshold levels of monochlorophenols causing odor in water have been reported to be as low as 0.33 to 2.0 µg/l for 2-chlorophenol (Hoak, 1957; Burttschell, et al. 1959), 100 to 1,000 µg/l for 3-chlorophenol (Hoak, 1957; Campbell, et al. 1958; Ruchoft and Ettinger, 1947), and 33 to 1,000 µg/l for 4-chlorophenol (Hoak, 1957; Burttschell, et al. 1959; Ruchoft and Ettinger, 1947). Threshold odor levels in water have also been reported to be 0.65 to 20 µg/l for dichlorophenols, 11 to 1,000 µg/l for trichlorophenols, 915 to 47,000 µg/l for tetrachlorophenols, and 857 to 12,000 µg/l for pentachlorophenol (Hoak, 1957; Burttschell, et al. 1959; Kinney, 1960; Ruchoft and Ettinger, 1947). It is apparent that the odor threshold progressively increases with an increase in substituted chlorine atoms.

The odor threshold of the cresols in water has been reported to be 71 µg/l, 333 µg/l and 45.4 µg/l for o-, m-, p-cresol, respectively, while the odor thresholds of the chlorinated cresols, 4-chloro- and 6-chloro-o-cresol, have been reported to be 75 µg/l and 3 µg/l, respectively (Hoak, 1957).

Several studies have reported the threshold concentrations of chlorinated phenols in water that impart unfavorable flavors in the edible portions of aquatic organisms (Schulze, 1961; Teal, 1959; Shumway, 1966). These threshold values in certain cases are lower than the odor threshold levels in water.

The threshold level of 2-chlorophenol in water causing taint in eel flesh and oysters has been reported to be 0.125 µg/l (Boetius, 1954). Although no data demonstrating the tainting properties of other specific chlorophenols and chlorocresols appears to be available, it is likely that they exhibit this property and probably follow a dose-effect relationship similar to that observed in the case of their odor producing properties.

Virtually no data are available on the bioconcentration or bioaccumulation of the lower chlorophenols and limited data are available regarding pentachlorophenol bioconcentration. Studies using 14C-labeled 2,4-dichlorophenol (DCP) demonstrated that oats and soybean seedlings concentrated DCP from dilute solutions (0.2 mg/l) by factors of 9.2 and 0.65-fold, respectively (Isensee and Jones, 1971). Bioconcentration data on pentachlorophenol may be found in the pentachlorophenol criterion document.

Chlorophenols, their sodium salts, and certain chlorocresols have been shown to be toxic to aquatic life, mammals, and man. In aquatic organisms it appears that the acute toxicity increases directly with the degree of chlorination. In addition, the production of odors in water and the tainting of fish flesh by the lower chlorophenols and chlorocresols has been reported to occur at extremely low concentrations. These findings, in conjunction with the potential pollution of chlorinated phenols from waste sources, inadvertent chlorination of phenols during disinfection, waste treatment degradation of herbicides and pesticides, and direct industrial and agricultural applications lead to the conclusion that chlorinated phenols represent a potential hazard to aquatic and terrestrial life.

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Aquatic Life Toxicology*

INTRODUCTION

A review of the available literature on the effects of chlorinated phenols on aquatic life is complicated by the variety of common and scientific names used for these compounds. A consistent set of names has been used herein and footnotes are used to identify other names that were used in referenced publications.

The toxicity of chlorinated phenols to aquatic life varies widely as a function of the nature and degree of ring substitution with chlorine. In general, the toxicity increases with increasing substitution and, in most cases, aquatic plants appear to be less sensitive to those chemicals than aquatic animals.

Because the toxicity of chlorinated phenols to various aquatic life forms is structure-dependent, giving rise to wide variability, it would be inappropriate to derive a criterion for these chemicals as a group. Instead, criteria should be derived on the basis of individual chemicals, when sufficient information becomes available.

In general, chlorinated phenols have been shown to impair the flavor of the edible portions of fishes at concentrations lower than those at which they are toxic to aquatic organisms.

EFFECTS

Acute Toxicity

Daphnia magna was less sensitive than the bluegill for five of the seven chlorinated phenols for which a comparison could be made and the acute values for Daphnia magna range from 290 µg/l for 2,3,4,6-tetrachlorophenol to 6,040 µg/l for 2,4,6-trichlorophenol (Table 1).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of the appropriate table are calculations for deriving various measures of toxicity as described in the Guidelines.

The 96-hour LC_{50} values for fathead minnows range from 30 µg/l for 4-chloro-3-methylphenol (U.S. EPA, 1972) to 9,040 µg/l for 2,4,6-trichlorophenol (Phipps, et al. Manuscript).

The 96-hour LC_{50} values for chlorinated phenols and the bluegill (U.S. EPA, 1978) are directly related to the degree of chlorination. These values decrease from 6,590 µg/l for 2-chlorophenol (see 2-chlorophenol criterion document) and 3,830 µg/l for 4-chlorophenol to 60 and 77 µg/l for pentachlorophenol (see pentachlorophenol criteria document).

All but one of the acute tests were run under static conditions and all but three without measured concentrations. Since many chlorinated phenols are only slightly soluble in water, and since some of the chemical could be expected to be absorbed by the animals and the testing environment, the above conditions could result in a low estimate of the toxicity.

Acute toxicity tests with saltwater invertebrate species consist of three 96-hour static tests with the mysid shrimp, and three chlorophenols (Table 1). Of these, 2,4,5-trichlorophenol was the most toxic with a 96-hour LC_{50} of 3,830 µg/l; the 96-hour LC_{50} for the least toxic compound was 29,700 µg/l for 4-chlorophenol.

Toxicity tests with the saltwater sheepshead minnow have also been conducted with the same three chlorophenols (Table 1). The 96-hour LC_{50} values range from 1,660 µg/l for 2,4,5-trichlorophenol to 5,350 µg/l for 4-chlorophenol (U.S. EPA, 1978).

Comparable data (U.S. EPA, 1978) are available for effects of other chlorinated phenols on fishes and invertebrate species (see criteria documents for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol for details). In general, toxicity of chlorophenols, except 2,3,5,6-tetra-chlorophenol with the mysid shrimp, appears to increase with increasing chlorination.

Chronic Toxicity

The only freshwater chronic data found were for 2,4,6-trichlorophenol (U.S. EPA, 1978). The chronic value was 720 µg/l from an early life stage test with the fathead minnow (Table 2). Additional data on the freshwater chronic toxicity of chlorinated phenols may be found in the criterion documents for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol.

The only saltwater chronic data were those from an early life stage test with the sheepshead minnow and 2,4-dichloro-6-methylphenol (Table 2). The lowest concentration tested, 360 µg/l, affected the fish in a 28-day exposure. Since no acute toxicity test was conducted with this chlorophenol, the value of this chronic test in formulating a water quality criterion is limited.

No chronic test has been conducted with any of the chlorinated phenols discussed in this document on any aquatic invertebrate species.

Plant Effects

The data in Table 3 indicate that freshwater aquatic plants are generally less sensitive to chlorinated phenols than fish or invertebrate species. The LC_{50} values for chlorosis for a series of ten chlorinated phenols (Blackman, et al. 1955) with *Lemna minor* ranged from 598,584 µg/l for 2-chloro-6-methylphenol and 282,832 µg/l for 4-chlorophenol to 603 µg/l for 2,3,4,6-tetrachlorophenol. Once again, the toxicity is related to increasing chlorination but not as clearly as noted for the bluegill. As with fish and aquatic invertebrate species, the derivation of a single criterion for all chlorinated phenols is inappropriate due to the wide variability in toxicity for this group of compounds.

Toxicity tests with chlorophenols and the saltwater alga, Skeletonema costatum, also revealed differences in toxicity, depending upon the compound tested (Table 3). Reductions in chlorophyll *a* and cell numbers showed that 2,3,5,6-tetrachlorophenol was the most toxic and 4-chlorophenol the least toxic.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorophenols and, as with the sheepshead minnow and mysid shrimp, toxicity generally increased with increased degree of chlorination.

Residues

No measured steady-state bioconcentration factors are available for the chlorinated phenols discussed in this document and aquatic organisms.

Miscellaneous

As stated in the introduction, chlorinated phenols have been shown to impair the flavor of freshwater fish flesh at concentrations much lower than those at which it has a toxic effect (Shumway and Palensky, 1973). In this study, rainbow trout were exposed for 48 hours to a range of concentrations of five different chlorinated phenols, and a panel of 15 judges scored the flavor of the cooked and coded fish samples on an increasing impairment scale of 0 to 6. The results were then plotted against exposure concentrations and graphically interpreted to arrive at an estimate of the highest concentration which would not impair the flavor of the flesh. The resulting estimates for five different compounds ranged from 23 µg/l for 2,5-dichlorophenol to 84 µg/l for 2,3-dichlorophenol (Table 4).

The additional toxicity data (Table 4) do not appear to differ significantly from the data already discussed.

Summary

The acute values for freshwater fish and invertebrate species ranged from 30 µg/l for the fathead minnow and 4-chloro-3-methyphenol to 9,040 µg/l for the same species and 2,4,6-trichlorophenol. Freshwater aquatic plants are generally less sensitive. One early life stage test yielded a chronic value of 720 µg/l for the fathead minnow and 2,4,6-trichlorophenol. Flesh-tainting data indicate that the edible portions of freshwater fishes may become tainted at water concentrations as low as 23 µg/l for rainbow trout and 2,5-dichlorophenol. In general, the acute toxicity of chlorinated phenols increases with amount of chlorination.

The data base for saltwater organisms is more limited with data only for the sheepshead minnow, mysid shrimp, and an algal species. The EC_{50} and LC_{50} values ranged from 440 to 29,700 µg/l with the algal species being the most sensitive. The pattern of increasing toxicity with increasing chlorination appears to be generally valid for saltwater species also.

CRITERIA

The available freshwater data for chlorinated phenols indicate that toxicity generally increases with increasing chlorination, and that acute toxicity occurs at concentrations as low as 30 µg/l for 4-chloro-3-methylphenol to greater than 500,000 µg/l for other compounds. Chronic toxicity occurs at concentrations as low as 970 µg/l for 2,4,6-trichlorophenol. Acute and chronic toxicity would occur at lower concentrations among species that are more sensitive than those tested.

The available saltwater data for chlorinated phenols indicate that toxicity generally increases with increasing chlorination, and that acute toxicity occurs at concentrations as low as 440 µg/l for 2,3,5,6-tetrachlorophenol and 29,700 µg/l for 4-chlorophenol. Acute toxicity would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of chlorinated phenols to sensitive saltwater aquatic life.

Table 1. Acute values for chlorinated phenols

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	4-chlorophenol	4,820	-	Kopperman, et al. 1974
Cladoceran, *Daphnia magna*	S, U	4-chlorophenol	4,060	4,420	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	2,4,5-trichlorophenol	2,660	2,660	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	2,4,6-trichlorophenol	6,040	6,040	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	2,3,5,6-tetrachlorophenol	570	570	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	2,3,4,6-tetrachlorophenol	290	290	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	4-chloro-2-methylphenol**	290	290	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	2,4-dichloro-6-methylphenol	430	430	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	S, M	2,4,6-trichlorophenol	600	-	U.S. EPA, 1972
Fathead minnow (juvenile), *Pimephales promelas*	FT, M	2,4,6-trichlorophenol	9,040	9,040	Phipps, et al. Manuscript
Fathead minnow, *Pimephales promelas*	S, M	4-chloro-3-methylphenol	30	30	U.S. EPA, 1972
Bluegill, *Lepomis macrochirus*	S, U	4-chlorophenol	3,830	3,830	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	2,4,5-trichlorophenol	450	450	U.S. EPA, 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S, U	2,4,6-trichlorophenol	320	320	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	2,3,4,6-tetrachlorophenol	140	140	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	2,3,5,6-tetrachlorophenol	170	170	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	4-chloro-2-methylphenol**	2,330	2,330	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	2,4-dichloro-6-methylphenol	1,640	1,640	U.S. EPA, 1978
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	S, U	4-chlorophenol	29,700	29,700	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	2,4,5-trichlorophenol	3,830	3,830	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	2,3,5,6-tetrachlorophenol	21,900	21,900	U.S. EPA, 1978
Sheepshead minnow, *Cyprindon variegatus*	S, U	4-chlorophenol	5,350	5,350	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	2,4,5-trichlorophenol	1,660	1,660	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	2,3,5,6-tetrachlorophenol	1,890	1,890	U.S. EPA, 1978

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* S = static, FT = flow-through, U = unmeasured, M = measured

**Data were reported for 4-chloro-6-methylphenol

Table 2. Chronic values for chlorinated phenols (U.S. EPA, 1978)

Species	**Method***	**Chemical**	**Limits (µg/l)**	**Species Mean Chronic Value (µg/l)**
		FRESHWATER SPECIES		
Fathead minnow, *Pimephales promelas*	ELS	2,4,6-trichlorophenol	530-970	720
		SALTWATER SPECIES		
Sheepshead minnow, *Cyprinodon variegatus*	ELS	2,4-dichloro-6-methylphenol	<360	-

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* ELS = early life stage

Acute-Chronic Ratio

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Fathead minnow, *Pimephales promelas*	2,4,6-trichlorophenol	9,040	720	13

Table 3. Plant values for chlorinated phenols

Species	Chemical	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Alga, *Chlorella pyrenoidosa*	Monochlorophenols	Complete destruction of chlorophyll	500,000	Huang & Gloyna, 1968
Alga, *Chlorella pyrenoidosa*	2,4,5- and 2,4,6-trichlorophenols	Complete destruction of chlorophyll	10,000	Huang & Gloyna, 1968
Alga, *Selenastrum capricornutum*	4-chlorophenol	96-hr EC50, cell production	4,790	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	2,4,5-trichlorophenol	96-hr EC50, chlorophyll *a*	1,220	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	2,3,5,6-tetrachlorophenol	96-hr EC50, cell production	2,660	U.S. EPA, 1978
Duckweed, *Lemna minor*	4-chlorophenol	Chlorosis (LC50)	282,832	Blackman, et al. 1955
Duckweed, *Lemna minor*	2,4,5-trichlorophenol	Chlorosis (LC50)	1,659	Blackman, et al. 1955
Duckweed, *Lemna minor*	2,4,6-trichlorophenol	Chlorosis (LC50)	5,923	Blackman, et al. 1955
Duckweed, *Lemna minor*	2,3,4,6-tetrachlorophenol	Chlorosis (LC50)	603	Blackman, et al. 1955
Duckweed, *Lemna minor*	4-chloro-2-methylphenol*	Chlorosis (LC50)	92,638	Blackman, et al. 1955
Duckweed, *Lemna minor*	2-chloro-6-methylphenol*	Chlorosis (LC50)	598,584	Blackman, et al. 1955
Duckweed, *Lemna minor*	4-chloro-3-methylphenol*	Chlorosis (LC50)	95,488	Blackman, et al. 1955
Duckweed, *Lemna minor*	2,6-dichloro-4-methylphenol*	Chlorosis (LC50)	65,479	Blackman, et al. 1955

Table 3. (Continued)

Species	Chemical	Effect	Result (µg/l)	Reference
Duckweed, *Lemna minor*	2,4,6-trichloro-3-methylphenol*	Chlorosis (LC50)	6,131	Blackman, et al. 1955
Duckweed, *Lemna minor*	2,4,5,6-tetrachloro-3-methylphenol*	Chlorosis (LC50)	1,107	Blackman, et al. 1955
		SALTWATER SPECIES		
Alga, *Skeletonema costatum*	4-chlorophenol	96-hr EC50, chlorophyll *a*	3,270	U.S. EPA, 1978
Alga, *Skeletonema costatum*	4-chlorophenol	96-hr EC50, cell count	3,560	U.S. EPA, 1978
Alga, *Skeletonema costatum*	2,4,5-trichlorophenol	96-hr EC50, chlorophyll *a*	890	U.S. EPA, 1978
Alga, *Skeletonema costatum*	2,4,5-trichlorophenol	96-hr EC50, cell count	960	U.S. EPA, 1978
Alga, *Skeletonema costatum*	2,3,5,6-tetrachlorophenol	96-hr EC50, chlorophyll *a*	440	U.S. EPA, 1978
Alga, *Skeletonema costatum*	2,3,5,6-tetrachlorophenol	96-hr EC50, cell count	550	U.S. EPA, 1978

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* In the original report, the methyl substituent was named first, and the chloro second.

Table 4. Other data for chlorinated phenols

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Lymnaeid snails, *Pseudosuccinea columella* and *Fossaria cubensis*	2,4,5-trichlorophenol	24 hrs	100% mortality	10,000	Batte & Swanson, 1952
Lymnaeid snails, *Pseudosuccinea columella* and *Fossaria cubensis*	Sodium 2,4,5-trichlorophenate (85%)	24 hrs	100% mortality	2,500	Batte & Swanson, 1952
Lymnaeid snails, *Pseudosoccinea columella* and *Fossaria cubensis*	2,4,6-trichlorophenol	24 hrs	100% mortality	5,000	Batte & Swanson, 1952
Rainbow trout, *Salmo gairdneri*	3-chlorophenol	48 hrs	Lowest concentration which killed 50% or more of the test fish	10,000	Shumay & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	4-chlorophenol	48 hrs	ETC*	45	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	2,3-dichlorophenol	48 hrs	ETC*	84	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	2,5-dichlorophenol	48 hrs	ETC*	23	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	2,6-dichlorophenol	48 hrs	ETC*	35	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	2,4,5-trichlorophenol	48 hrs	Lowest concentration which killed 50% or more of the test fish	1,000	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	2,4,6-trichlorophenol	48 hrs	ETC*	52	Shumway & Palensky, 1973
Goldfish, *Carassius auratus*	3-chlorophenol	8 hrs	62% mortality	20,600	Gersdorff & Smith, 1940

Table 4. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Goldfish, Carassius auratus	4-chlorophenol	8 hrs	54% mortality	6,300	Gersdorff & Smith, 1940
Goldfish, Carassius auratus	4-chlorophenol	24 hrs	LC50	9,000	Kobayashi, et al. 1979
Goldfish, Carassius auratus	2,4,5-trichlorophenol	24 hrs	LC50	1,700	Kobayashi, et al. 1979
Goldfish, Carassius auratus	2,4,6-trichlorophenol	24 hrs	LC50	10,000	Kobayashi, et al. 1979
Goldfish, Carassius auratus	2,3,4,6-tetrachlorophenol	24 hrs	LC50	750	Kobayashi, et al. 1979

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* ETC = the highest estimated concentration of material that will not impair the flavor of the flesh of exposed fish.

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3-CHLOROPHENOL AND 4-CHLOROPHENOL

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Monochlorophenol has three isomeric forms, each distinguished by the position of the chlorine atom relative to the hydroxyl group on carbon one of the benzene ring. The three isomers are 2-chlorophenol or o-chlorophenol; 3-chlorophenol or m-chlorophenol; and 4-chlorophenol or p-chlorophenol. This document will discuss only 3-and 4-chlorophenol since 2-chlorophenol was addressed in a separate criteria document.

Monochlorophenols have been used as antiseptics since 1893 (von Oettingen, 1949). They occur as intermediates in the formation of other chlorophenol-containing products and as metabolic breakdown products of other chlorophenols or chlorobenzene. They may also be formed by the chlorination of water containing natural phenol or phenolic wastes.

The chemical properties of 3- and 4-chlorophenol are listed in Table 1. One important property is the ability of relatively low concentrations of chlorophenols to produce a medicinal odor and taste in water. This low organoleptic threshold may call attention to a state of contamination and aid in protecting humans from unacceptable levels of exposure.

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to establish water levels of 300-960 µg/l. Phenols are found in raw domestic sewage at levels of 70-100 µg/l. Complex phenols are

TABLE 1

Properties of Monochlorophenols

3-Chlorophenol

Alternate name	m-chlorophenol
Molecular weight	128.56
Specific gravity	1.268
Form at room temperature	needles
Melting point	32°C
Boiling point	214°C
Solubility	
water	slightly soluble
alcohol	soluble
ether	soluble
benzene	very soluble
Vapor pressure	1 mm Hg at 44.2°C
CAS number	000108430
Odor threshold in water-20 to 22°C	50 μg/l (Deitz and Traud, 1978)
Taste threshold in water-20 to 22°C	0.1 μg/l (Deitz and Traud, 1978)

4-Chlorophenol

Alternate name	p-chlorophenol
Molecular weight	128.56
Specific gravity	1.306
Form at room temperature	needles
Melting point	41°C
Boiling point	217°C
Solubility	
water	very slightly soluble
alcohol	very soluble
ether	very soluble
benzene	very soluble
Vapor pressure	1 mm Hg at 49.8°C
CAS number	000106489
Odor threshold in water-30°C	33 μg/l (Hoak, 1957)
Taste threshold in water-20 to 22°C	0.1 μg/l (Dietz and Traud, 1978)

at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme, 2- and 4-chlorophenol are formed early. These molecules are further chlorinated to 2,6- or 2,4-dichlorophenol. The final product is 2,4,6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's study consisted of less than 5 percent each of 2- and 4-chlorophenols, 25 percent 2,6-dichlorophenol, 20 percent 2,4-dichlorophenol and 40 to 50 percent 2,4,6-trichlorophenol.

EXPOSURE

Ingestion from Water

Burttschell, et al. (1959) demonstrated that the chlorination of water containing phenol could result in the formation of chlorophenols including mono-, di-, and trichlorophenol isomers. Piet and De Grunt (1975) found monochlorophenols in surface waters in the Netherlands at concentrations of 2 to 20 μg/l (ppb). A level of 20 μg/l in water, consumed at a rate of 2 l/day by a 70 kg individual, would result in a daily exposure of 0.57 μg/kg.

Another source of chlorophenols in water is the chlorination of sewage. Jolley, et al. (1975) analyzed chlorinated sewage treatment plant effluents and found 3-chlorophenol at 0.5 μg/l and 4-chlorophenol at 0.7 μg/l. Ingols, et al. (1966) studied the biological degradation of chlorophenols in activated sludge. Both

3- and 4-chlorophenol at levels of 100 mg/l were completely degraded in three days with 100 percent ring degradation.

Alexander and Aleem (1961) studied the microbial decomposition of chlorophenols in soil suspensions. 3-Chlorophenol did not disappear completely in 47 or 72 days when tested with two soil types. 4-Chlorophenol disappeared in 3 or 9 days in the same two soil types.

The association of unpleasant taste or odor of tap water with chlorophenols has been of interest for a number of years (Hoak, 1957; Burttschell, et al. 1959; Campbell, et al. 1958; Deitz and Traud, 1978). Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2-0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for chlorophenols in water are shown in Table 2.

Odor and taste thresholds for chlorophenols in water have been reported by a number of investigators (Hoak, 1957; Dietz and Traud, 1978; Burttschell, et al. 1959). Hoak (1957) reported the odor threshold of phenol and 19 phenolic compounds. In a study conducted at the Mellon Institute in Pittsburgh, Pennsylvania, a panel of 2 or 4 persons sniffed samples of pure phenolic compounds in odor-free water, which had been heated to 30 or 60°C. A flask of plain odor-free water was provided for comparison. The various samples were placed in random order before the test persons, and the flask with the lowest perceptible odor was noted by each

TABLE 2

Summary of Odor Thresholds for Monochlorophenols in Water

	Threshold-ppb		Reference
	(µg/l)	(°C)	
2-chlorophenol	0.33	30	1
	2	25	2
	10	20-22	3
3-chlorophenol	200	30	1
	50	20-22	3
4-chlorophenol	33	30	1
	250	25	2
	60	20-22	3

1 - Hoak, 1957
2 - Burttschell, et al. 1959
3 - Deitz and Traud, 1978

individual sniffer. The lowest concentration detected was considered to be the threshold of the chemicals tested. Chlorinated phenols were the compounds most easily detected. The odor thresholds reported for 3-and 4-chlorophenol were 200 µg/l and 33 µg/l, respectively (Table 2).

Deitz and Traud (1978) used a panel composed of 9 to 12 persons of both sexes and various age groups to test the organoleptic detection thresholds for 126 phenolic compounds. To test for odor thresholds, 200 ml samples of the different test concentrations were placed in stoppered odor-free glass bottles, shaken for approximately five minutes, and sniffed at room temperature (20 to 22°C). For each test, water without the phenolic additive was used as a background sample. The odor tests took place in several individual rooms in which phenols and other substances with intense odors had not been used previously. Geometric mean values were used to determine threshold levels. Odor detection thresholds are summarized in Table 2. To determine taste threshold concentrations of selected phenolic compounds, a panel of four test individuals tasted water samples containing various amounts of phenolic additives. As a point of comparison, water without phenolic additives was tasted first. Samples with increasing phenolic concentrations were then tested. Between samples, the mouth was rinsed with the comparison water and the test person ate several bites of dry white bread to "neutralize" the taste. Geometric mean detection level values for 3- and 4-chlorophenol indicated threshold levels of 0.1 µg/l for taste for both chemicals.

Burttschell, et al. (1959) made dilutions of chlorophenols including 3- and 4-chlorophenol in carbon-filtered tap water and used a panel of from 4 to 6 persons to evaluate odor and taste. Tests were carried out at room temperature, which the investigator estimated to be 25°C. If a panel member's response was doubtful, the sample was considered negative. The geometric mean of the panel responses was used as the odor threshold. The odor detection threshold for 4-chlorophenol was 250 µg/l (Table 2).

Ingestion from Food

The threshold concentrations of the monochlorophenols in water that impart an offensive flavor to the edible portion of the flesh of aquatic organisms have been reported. A summary of the data is presented in Table 3.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these

TABLE 3

Summary of Threshold Concentrations of Monochlorophenols in Water that Cause Tainting of the Flesh of Aquatic Organisms

Compound	Threshold (μg/l)	Reference
2-chlorophenol	15.0	1
	15.0	2
3-chlorophenol	60.0	1
4-chlorophenol	60.0	1
	50.0	2

1 - Schulze, 1961
2 - Teal, 1959

data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state BCF is available for 3- or 4-chlorophenol, but the equation "Log BCF = (0.85 Log P - 0.70" can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids from the octanol-water partition coefficient (P). A measured log P value of 2.4 for 4-chlorophenol was obtained from Hansch and Leo (1979). The adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCF for the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 8.6.

Inhalation

Pertinent data could not be located in the available literature regarding the presence of monochlorophenols in air.

Dermal

Roberts, et al. (1977) used human epidermal membranes obtained at autopsy in an *in vitro* test system to determine the permeability of the human skin to various chemicals. 4-Chlorophenol was shown to permeate the skin, and to produce damage at a threshold concentration of 0.75 percent (w/v).

PHARMACOKINETICS

No systematic studies of the pharmacokinetics of 3- or 4-chlorophenol in man or laboratory animals were found. However, Karpow (1893) reported that 87 percent of 4-chlorophenol was excreted in urine of dogs as sulfuric and glucuronic acid conjugates.

The ingestion of chlorobenzene may also give rise to an internal metabolic exposure to chlorophenol. The mammalian metabolism of chlorobenzene yields 2-, 3-, and 4-chlorophenol as the major products (Smith, et al. 1972).

EFFECTS

Acute, Subacute, and Chronic Toxicity

The acute oral, subcutaneous (s.c.), dermal, intraperitoneal (i.p.), and inhalation LD_{50}s for 3- and 4-chlorophenol are shown in Table 4. Because 3-chlorophenol is a liquid at room temperature, some of the early workers reported LD_{50}s as ml/kg. The oral LD_{50} for each isomer is on the order of 500 to 900 mg/kg. The dermal LD_{50} for 4-chlorophenol is 1,500 mg/kg, indicating dermal absorption. Interestingly, both 3- and 4-chlorophenol are less toxic when given subcutaneously than when taken orally. This may reflect a slower absorption from the injection site and/or rapid metabolism of the absorbed compounds.

4-Chlorophenol applied dermally causes skin irritation and necrosis in rabbits, rats, and guinea pigs. Dermal exposure can result in convulsive seizures (Gurova, 1964).

Cats survived four doses of 40 mg/kg of 4-chlorophenol administered intraperitoneally at 3-hour intervals (Miller, et al. 1973).

TABLE 4

Acute Toxicity of Monochlorophenols

Chemical	Solvent	Species	Toxic Response	Reference
3-chlorophenol	olive oil	rat	oral LD_{50} = 0.56 ml/kg	Deichmann and Mergard, 1948
	olive oil	rat	s.c. LD_{50} = 1.39 ml/kg	Deichmann and Mergard, 1948
	olive oil	rat	i.p. LD_{50} = 335 mg/kg	Farquharson, et al. 1958
4-chlorophenol	not stated	rat	oral LD_{50} = 500 mg/kg	Gurova, 1964
	olive oil	rat	oral LD_{50} = 660 mg/kg	Deichmann and Mergard, 1948
	not stated	mouse	oral LD_{50} = 860 mg/kg	Schrotter, et al. 1977
	olive oil	rat	s.c. LD_{50} = 1,030 mg/kg	Deichmann and Mergard, 1948
	not stated	rat	der. LD_{50} = 1,500 mg/kg	Gurova, 1964
	olive oil	rat	i.p. LD_{50} = 250 mg/kg	Farquharson, et al. 1958
		mouse	inh. LC_{50} = 11 mg/m^3	Gurova, 1964

The monochlorophenols act on the nervous system to produce tremors and convulsions, an effect reported several times in the literature. The monochlorophenols with a pKa of 8 or greater are convulsants. At body pH (7.0 to 7.4), these chlorophenols are largely undissociated.

Binet (1896) reported that subcutaneous injections of monochlorophenols in rats and guinea pigs caused muscle twitching, spasms, generalized tremors, weakness, staggering, and finally collapse. Kuroda (1926) found that intravenous doses of 100 mg/kg of any of the three monochlorophenol isomers caused convulsions in rabbits. In acutely toxic doses, 3-chlorophenol causes restlessness and increased respiration followed by rapidly developing motor weakness (Deichmann, 1943). Chronic convulsive seizures follow and continue until death. The clinical signs are similar with 4-chlorophenol but the convulsions are more severe.

Farquharson, et al. (1958) also reported that 2-, 3-, or 4-chlorophenol produced convulsive seizures in rats. Body temperature was reduced 2 to 5°C, and rigor mortis did not develop within five minutes of death as with tri-, tetra-, and pentachlorophenols. Death occurred one hour after administration of the LD_{50} to rats. At higher doses, deaths occurred in 5 to 15 minutes. There were no further deaths in rats surviving three hours. Convulsions occurred as soon as 1 to 2 minutes following intraperitoneal injection. 4-Chlorophenol and 3-chlorophenol also stimulated oxygen uptake by rat brain homogenate at concentrations between 2.5×10^{-5} and 1×10^{-3}M.

Angel and Rogers (1972) used urethane-anesthetized mice to determine the intraperitoneal dose required to produce convulsions in 50 percent of the test animals, i.e., the CD_{50}. The CD_{50}s were 100.6 mg/kg for 3-chlorophenol and 115.7 mg/kg for 4-chlorophenol. Both of these monochlorophenols have approximately 1.2 times the convulsant potency of phenol. These CD_{50} values are approximately one-half to one-third of the intraperitoneal LD_{50}.

Gurova (1964) conducted inhalation studies of 4-chlorophenol using mice and rats. The inhalation LC_{50} for mice was 11 mg/m^3, with the duration of exposure not reported. Single inhalations of 20 mg/m^3 did not produce acute poisoning in rats. Rats exposed to 13 mg/m^3 for two hours showed increased neuromuscular excitability based on response to peripheral nerve electrical stimulation. These animals also experienced increased oxygen consumption. Mice were more sensitive since 2 mg/m^3 increased their oxygen consumption.

Gurova (1964) additionally reported a study in which rats and mice inhaled 4-chlorophenol in supraliminal concentrations for 4-hour periods for 28 days. Considerable changes in the morphology of the internal organs of killed animals were observed. These changes included congestion and focal hemorrhages in the brain, lungs, liver, and myocardium, as well as thickening of the alveolar septa and some atelectasis and emphysema in the lungs.

Rats exposed 6 hrs/day for four months to 2 mg/m^3 showed a weight loss during the first 30 days followed by an increased weight gain. These animals also showed an increased myoneural excitability. Body temperature, hemoglobin, RBC, WBC, and sedimentation rate were not altered. Microscopic examination of organs of killed animals revealed only slight congestion; minor fibrotic changes in the alveolar septa which were noted in some animals.

Banna and Jabbur (1970) studied the effects of phenols on nerve synaptic transmission in cats. Phenol, like the monochlorophenols, is a convulsant. The mechanism of action apparently involves an increase in the amount of neurotransmitter released at the nerve synapse.

In terms of mechanism of action studies, most efforts have been directed toward effects on oxidative phosphorylation and enzymes involved in carbohydrate and intermediary metabolism and ATP.

Parker (1958) studied the effect of chlorophenols on isolated rat liver mitochondria metabolism. 2,4-Dinitrophenol was used as a reference compound because of its known ability to uncouple oxidative phosphorylation. 4-Chlorophenol at 2.8×10^{-4}M had 21 percent of the activity of 2×10^{-5}M of 2,4-dinitrophenol.

Mitsuda, et al. (1963) studied the effects of various chlorophenols on oxidative phosphorylation of isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, with 0.05 ml of mitochondrial suspension containing 0.43 mg N. The ID_{50} (concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP) was determined. The ID_{50} values for the monochlorophenols were 520 µM, 150 µM, and 180 µM for 2-, 3-, and 4-chlorophenol, respectively. For comparison, the ID_{50}s for pentachlorophenol and 2,4-dinitrophenol are 1 µM and 17 µM, respectively.

Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation *in vitro*. 3-Chlorophenol and 4-chlorophenol caused complete uncoupling at 2.5 mM. For comparison, the known uncoupler 2,4-dinitrophenol completely uncoupled the test system at 0.1 mM. There was a positive relationship between mitochondrial protein binding and uncoupling properties.

During the past years, one research group has developed a novel approach to studying the potential effects of chemicals on the eye. Ismail, et al. (1976) studied the permeation of a number of chemicals, including 2-chlorophenol into the bovine lens capsule and examined the subsequent effects on lens enzymes. Their hypothesis was that environmental chemicals may be responsible for eye diseases or lens opacities. 3,4-Dichlorophenol was found to rapidly permeate the lens capsule. Using a 3,4-dichlorophenol concentration of 10^{-4}M (16 mg/l), the activities of various enzymes in the bovine lenses were compared with those of the control lenses. No statistical analysis was reported; the results are presented in Table 5. For comparison, the activity of 2-chlorophenol, the only other chlorophenol tested, is also presented. The response pattern is complex and difficult to interpret in the absence of statistical analysis.

Korte, et al. (1976) have used the isolated bovine lens system to study the metabolic effects of various chemicals on this part of the eye. One lens is used as a control and the other as the experimental. 4-Chlorophenol at 10^{-3}M reduced ATP, glucose-6-phosphate, and glucose and fructose levels after a 48-hour incubation. 3-Chlorophenol reduced levels of fructose, ATP and ADP, and

TABLE 5

Effect[a] of Chlorophenols on Enzyme Activities of Isolated Bovine Lenses*

Enzyme	2-chlorophenol[b]	3,4-dichlorophenol[b]
Lactic dehydrogenase	94.0	85.5
Malate dehydrogenase	64.4	86.3
Sorbitol dehydrogenase	91.9	107.3
Glucose-6-phosphate dehydrogenase	129.9	70.0
Fructose-diphosphate aldolase	80.4	85.7
Pyruvate kinase	92.9	99.0
Glutamate-oxalacetate-transaminase	92.7	111.9
Flutamate-pyruvate-transaminase	142.9	92.9

*Source: Ismail, et al. 1976

[a] The effect is expressed as percent of control

[b] Each chemical was tested at $10^{-4}M$

increased AMP levels. Korte, et al. (1976) did not find changes in the following dehydrogenases: lactate, malate, sorbitol, glucose-6-phosphate, or in fructose 1,6-diphosphate aldolase or pyruvate kinase.

Harrison and Madonia (1971) pointed out that 4-chlorophenol has been used since the nineteenth century at a concentration of 35 percent in camphor for endodontic therapy in dentistry. They conducted ocular and dermal toxicity tests with 1 or 2 percent aqueous solutions of 4-chlorophenol and 35 percent camphorated 4-chlorophenol. The 1 percent aqueous solution caused slight hyperemia when 0.15 ml was placed on the cornea of white rabbits. A 2 percent aqueous solution (0.15 ml) produced a more severe response, characterized by moderate to severe hyperemia, mild to moderate edema, cloudy cornea and exudation. The 35 percent camphorated 4-chlorophenol produced a severe response. The changes induced by the 1 percent and 2 percent aqueous solutions became evident after five minutes, were most intense after five hours, and subsided by 96 hours post-administration. Harrison and Madonia also injected 0.1 ml of each solution intradermally in rabbits. The 1 and 2 percent aqueous parachlorophenol solutions produced mild inflammation after 24 and 72 hours. The 35 percent camphorated 4-chlorophenol caused a severe inflammatory response including necrosis.

Gurova (1964) reported the effects of 4-chlorophenol in industrial workers in an aniline dye plant in Russia. Air levels ranged from 0.3 to 21 mg/m^3 depending on the work site and operation. Two accidental acute poisonings were reported with clinical signs consisting of headache, dizziness, respiratory disorder, vomiting, loss of coordination, tremor and, in one case, liver enlargement.

Other workers not acutely affected reported experiencing headache, dizziness, weakness, nausea, vomiting, and paresthesia (abnormal prickling sensation). A health survey was done comparing workers exposed to 4-chlorophenol with unexposed workers in the same plant. The 4-chlorophenol workers had a significantly higher incidence of neurologic disorders. Symptoms reported included neurasthenia (nervous exhaustion), insomnia, irritability, frequent mood changes and rapid fatigability. Peripheral nerve stimulation studies showed increased myoneural excitability in exposed workers. A decreased response to a two-point touch discrimination was apparent, in that the minimum detection distance between the points was increased. Changes in the capillaries of the nail fold of the fingers were said to occur, but were not described. An average permissible air concentration of 3 mg/m^3 was reported for industrial workers.

Synergism and/or Antagonism, Teratogenicity, and Mutagenicity

Pertinent data could not be located in the available literature.

Carcinogenicity

Adequate information was not found to determine whether 3- or 4-chlorophenol possess carcinogenic properties.

Boutwell and Bosch (1959) conducted a series of experiments on the tumor promoting action of substituted phenols using repeated applications of concentrated solutions to the backs of mice. A 20 percent solution of 3-chlorophenol in benzene increased the number of papillomas, but no carcinomas were found after 15 weeks (Table 6). The tumor initiator DMBA (9,10-dimethyl-1,2-benzanthracene) was used. Papillomas occurred at the application site.

TABLE 6

Papilloma Promoting Action of 3-Chlorophenol[a]*

	Group	
	Control	3-chlorophenol (20%)
Number of mice (survivors/original)	15/20	21/33
Average number of papillomas per survivor	0.07	1.38
Percent survivors with papillomas	7	67
Percent survivors with carcinomas	0	0

*Source: Boutwell and Bosch, 1959

[a] Promoter applied twice weekly. Initiator 0.3% DMBA in benzene. Promoter in benzene.

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not yet been established for 3-chlorophenol or 4-chlorophenol.

Current Levels of Exposure

Pertinent data could not be located in the available literature concerning current exposure levels of 3- and 4-chlorophenol.

Special Groups at Risk

Pertinent data could not be located in the available literature concerning groups at special risk of exposure to 3- or 4-chlorophenol.

Basis and Derivation of Criterion

Insufficient data exist to indicate that 3-chlorophenol is carcinogenic. The only study performed (Boutswell and Bosch, 1959) was designed to detect the promoting activity of 3-chlorophenol with dimethylbenzanthracene (DMBA). In this study, 3-chlorophenol exhibited promoting activity in the formation of papillomas.

A paucity of information pertaining to the acute or chronic effects of 3-chlorophenol or 4-chlorophenol precludes the possibility of deriving a health effects-based criterion level for these compounds. Consequently, the recommended criterion is based on organoleptic properties.

Monochlorinated phenols have been shown to impart a medicinal taste and odor to water and to fish residing in contaminated waters (Schultze, 1961; Teal, 1959; Dietz and Traud, 1978; Burttschell, et al. 1959; Hoak, 1957). Data from the available studies of odor detection thresholds of 3- and 4-chlorophenols indicate threshold ranges of 50 to 200 µg/l and 33 to 250 µg/l, respectively (see Table 2). Within these ranges, also lie the threshold concentrations for tainting of the flesh of aquatic organisms residing in contaminated waters (see Table 3). Dietz and Traud (1978) have also determined the taste and odor threshold concentrations of 36 phenolic compounds, including 3- and 4-chlorophenols, in water. The odor threshold values obtained for these compounds were 50 and 60 µg/l, respectively. The taste threshold value obtained by these authors for both 3- and 4-chlorophenols was 0.1 µg/l.

The taste threshold determined by Dietz and Traud (1978) for the detection of 3-chlorophenol and 4-chlorophenol in water is used as the basis for the ambient water quality criterion. The Deitz and Traud study was chosen for a number of reasons. These authors present a recent study involving well-defined procedures and a number of documented controls. This study utilized "fresh" water from the base outlet of the Verse Dam (Germany) for all experiments. The water was described as clear and neutral with respect to both odor and taste. These conditions are considered to more closely approximate the conditions of ambient water found in lakes, rivers, and streams than would those of the Hoak (1957) and Burttschell, et al. (1959) studies, which utilized carbon-filtered laboratory distilled water. The 20 to 22°C temperature of the water in the Dietz and Traud odor and taste tests might also more closely approximate the temperature at which water is normally consumed than do the 30°C or 25°C temperatures used in the studies of Hoak (1957) and Burttschell, et al. (1959), respectively. However, it is recognized that the temperature of water consumed by humans is quite obviously variable, and no study will represent the temperature of water consumed by all Americans.

Thus, based on the prevention of adverse organoleptic effects, the criterion recommended for 3-chlorophenol and 4-chlorophenol is 0.1 µg/l. It is emphasized that this is a criterion based on aesthetic rather than health effects. Data on human health effects must be developed as a more substantial basis for recommending a criterion for the protection of human health.

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2,3-DICHLOROPHENOL

2,5-DICHLOROPHENOL[2,6-DICHLOROPHENOL[

3,4-DICHLOROPHENOL AND 4,6-DICHLOROPHENOL

Mammalian Toxicology and Human Health Effects

INTRODUCTION

There are several isomers of dichlorophenol. The most common is 2,4-dichlorophenol, which is reviewed in another document in this series. The remaining dichlorophenol isomers apparently have not found use as primary chemicals. The following isomers are discussed in this document: 2,3-, 2,5-, 2,6-, 3,4-, and 4,6-dichlorophenol. Physiochemical properties of these compounds are listed in Table 1. The dichlorophenols can be formed either as intermediates in the chlorination of phenol to higher chlorophenols, or as degradation products. A limited amount of work has been reported on dichlorophenols other than the 2,4-isomer.

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to establish water levels of 300 to 960 µg/l. Phenols are found in raw domestic sewage at levels of 70 to 100 µg/l. Complex phenols are at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme, 2- and 4-chlorophenol are formed early. These molecules are further chlorinated to 2,6- or 2,4-dichlorophenol. The final product is

TABLE 1

Physiochemical Properties*

Property	Dichlorophenol Isomer			
	2,5-	2,6-	3,4-	3,5-
Molecular weight	163	163	163	163
Formula	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$
Melting point ^oC	59	68-9	68	68
Boiling point ^oC	211	219	253	233
Solubility				
water	slightly	-	slightly	slightly
alcohol	very	very	very	very
ether	very	very	very	very
benzene	soluble	soluble	soluble	-
Vapor pressure	-	1mm Hg, 59^oC	-	-
CAS number	-	87-65-0	-	-

*Weast, (ed.) 1978

2,4,6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's study consisted of less than 5 percent each of 2- and 4-chlorophenols, 25 percent 2,6-dichlorophenol, 20 percent 2,4-dichlorophenol and 40 to 50 percent 2,4,6-trichlorophenol.

Crosby and Wong (1973) reported that the photodecomposition of the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) results in the formation of small amounts of 2,5-dichlorophenol.

EXPOSURE

Ingestion from Water

Piet and DeGrunt (1975) found unspecified dichlorophenol isomers in Dutch surface waters at concentrations of 0.01 to 1.5 μg/l. Burttschell, et al. (1959) demonstrated that the chlorination of phenol-laden water could result in the formation of mono-, di-, and trichlorophenol isomers.

Ingols, et al. (1966) studied the biological degradation of chlorophenols in activated sludge. 2,5-Dichlorophenol was more resistent to degradation than 2,4-dichlorophenol. While 2,4-dichlorophenol was 100 percent degraded, including ring degradation, in five days, 2,5-dichlorophenol was only 52 percent ring-degraded in four days.

Alexander and Aleem (1961) determined the microbial decomposition of 2,5-dichlorophenol in a Dunkirk soil suspension. Disappearance was not complete at the end of 72 days.

The association of unpleasant taste or odor of tap water with chlorophenols has been of interest for a number of years (Hoak, 1957; Burttschell, et al. 1959; Campbell, et al. 1958). Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2 to 0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for dichlorophenols in water are shown in Table 2. Taste threshold data are summarized in Table 3.

Odor and taste thresholds for chlorinated phenols in water have been reported by a number of authors (Hoak, 1957; Dietz and Traud, 1978; Burttschell, et al. 1959). These studies are discussed in the Monochlorophenols portion of this document (see Ingestion from Water).

Ingestion from Food

Pertinent data could not be located in the available literature.

Inhalation

Olie, et al. (1977) reported finding di-, tri- and tetrachlorphenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

Pertinent data could not be located in the available literature.

PHARMACOKINETICS

Pharmacokinetic data specific to the dichlorophenol isomers discussed in this document were not available. It is reasonable to assume that dichlorophenol isomers are absorbed through the skin and from the gut, and rapidly eliminated from the body, as are other chlorophenols.

TABLE 2

Comparison of Odor Thresholds for Dichlorophenols in Water

	Threshold-ppb		Reference
	(μg/l)	(°C)	
2,3-dichlorophenol	30	20-22	3
2,4-dichlorophenol	0.65	30	1
	2	25	2
	40	20-22	3
2,5-dichlorophenol	33	30	1
	30	20-22	3
2,6-dichlorophenol	3	25	2
	200	20-22	3
3,4-dichlorophenol	100	20-22	3

1 - Hoak, 1957
2 - Burttschell, et al. 1959
3 - Deitz and Traud, 1978

TABLE 3

Summary of Taste Threshold Concentrations of Dichlorophenols in Water

Compound	Threshold (μg/l)	Reference
2,3-dichlorophenol	0.04	1
2,4-dichlorophenol	0.3	1
	8.0	2
2,5-dichlorophenol	0.5	1
2,6-dichlorophenol	0.2	1
	2.0	2
3,4-dichlorophenol	0.3	1

1 - Deitz and Traud, 1978
2 - Burttschell, et al. 1959

Metabolism

Dichlorobenzenes are metabolized by mammals to dichlorophenols (Kohli, et al. 1976). For example, 1,2-dichlorobenzene gives rise to 3,4-dichlorophenol and smaller amounts of 2,3- and 4,5-dichlorophenols and 3,4-dichlorophenylmercapturic acid.

Foster and Saha (1978) reported that chicken liver homogenates would metabolize lindane and the alpha and delta but not the beta isomers of 1,2,3,4,5,6, hexachlorocyclohexane. The metabolic products included 2,4,6-trichlorophenol, 2,3-dichlorophenol as well as di- and trichlorobenzenes.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Farquharson, et al. (1958) reported that 2,6-dichlorophenol produced convulsions in rats. The intraperitoneal LD_{50} was 390 mg/kg. Rats given the LD_{50} died within one hour; deaths did not occur later in rats surviving at least three hours. Body temperature was depressed by $0.7^{o}C$, and rigor mortis did not occur within five minutes of death as it does with higher chlorinated phenols. Oxygen consumption by rat brain homogenate was stimulated at concentrations between 2.5×10^{-5} and 1×10^{-3} M.

Banna and Jabbur (1970) studied the effects of phenols, but not chlorophenols directly, on nerve synaptic transmission in cats. Phenol is a convulsant, as are the lower chlorinated phenols. Experimental results suggest that the mechanism of action involves an increase in the amount of neurotransmitter released at the new synapse.

Studies on the mechanism of action of chlorophenols have primarily focused on effects on oxidative phosphorylation. Korte, et al. (1976) studied the effect of 3,4-dichlorophenol on carbohydrate metabolism and enzyme activity in the incubated bovine lens. At a concentration of 10^{-3} M, 3,4-dichlorophenol decreased ATP and ADP levels while increasing AMP levels. There was no effect on glucose or fructose-6-phosphate levels. Activities of malate dehydrogenase, glucose-6-phosphate dehydrogenase and pyruvate kinase were reduced. The dichlorophenol caused swelling of the lens.

Ismail, et al. (1976) studied the permeation of chemicals into the bovine lens capsule and the effects on lens enzymes. Their hypothesis was that environmental chemicals may be responsible for eye diseases or lens opacities. 3,4-Dichlorophenol was found to permeate the lens capsule rapidly. Using a concentration of 10^{-4} M (16 mg/l) of 3,4-dichlorophenol, the activity of various enzymes in the bovine lenses was compared with control lenses. The results are presented in Table 4. For comparison, data on the effect of 2-chlorophenol, the only other chlorophenol tested, are presented. The response pattern is complex and difficult to interpret in the absence of statistical analysis.

Synergism and/or Antagonism and Teratogenicity

Pertinent data could not be located in the available literature.

Mutagenicity

Rasanen and Hattula (1977) tested chlorophenols for mutagenicity using the *Salmonella*-mammalian microsome Ames assay in both activated and nonactivated systems. The following

TABLE 4

Effect[a] of Chlorophenols on Enzyme Activities of Isolated Bovine Lenses*

Enzyme	2-chlorophenol[b]	3,4-dichlorophenol[b]
Lactic dehydrogenase	94.0	85.5
Malate dehydrogenase	64.4	86.3
Sorbitol dehydrogenase	91.9	107.3
Glucose-6-phosphate dehydrogenase	129.9	70.0
Fructose-diphosphate aldolase	80.4	85.7
Pyruvate kinase	92.9	99.0
Glutamate-oxalacetate-transaminase	92.7	111.9
Flutamate-pyruvate-transaminase	142.9	92.9

*Source: Ismail, et al. 1976

[a] The effect is expressed as percent of control

[b] Each chemical was tested at 10^{-4}M

dichlorophenol isomers were tested and reported as non-mutagenic in both test systems: 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-dichlorophenols. Mutagenicity in mammalian test systems has not been evaluated.

Carcinogenicity

Pertinent data could not be located in the available literature.

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not been established for the dichlorophenols.

Current Levels of Exposure

Pertinent data could not be located in the available literature concerning current exposure levels of dichlorophenols.

Special Groups at Risk

Pertinent data could not be located in the available literature concerning groups at special risk of exposure to dichlorophenols.

Basis and Derivation of Criterion

A paucity of information pertaining to the acute or chronic effects of dichlorophenols precludes the possibility of deriving a health effects based criterion level for these compounds. Consequently, the recommended criteria are based on organoleptic properties.

Dichlorophenols have been shown to impart a medicinal taste and odor to water (Hoak, 1957; Deitz and Traud, 1978). Details of the Hoak (1957), Burttschell, et al. (1959), and Deitz and Traud (1978) studies are discussed in the section of this document dealing with monochlorophenols. Data from the available studies of odor detection thresholds of dichlorophenols are summarized in Table 2. Deitz and Traud (1978) have determined the taste and odor threshold concentrations of 36 phenolic compounds, including dichlorophenols, in water. The taste and odor threshold values for dichlorophenols are summarized in Tables 2 and 3.

The taste thresholds determined by Dietz and Traud (1978) for the detection of the various dichlorophenols in water are used as the bases for the ambient water quality criteria. The Dietz and Traud study was chosen for a number of reasons. These authors present a recent study involving well-defined procedures and a number of documented controls. This study utilized "fresh" water from the base outlet of the Verse Dam (Germany) for all experiments. The water was described as clear and neutral with respect to both odor and taste. These conditions are considered to more closely approximate the conditions of ambient water found in lakes, rivers, and streams than would those of the Hoak (1957) and Burttschell, et al. (1959) studies, which utilized carbon-filtered laboratory distilled water. The 20 to 22°C temperature of the water in the Dietz and Traud odor and taste tests might also more closely approximate the temperature at which water is normally consumed than do the 30°C or 25°C temperatures used in the studies of Hoak (1957) and Burttschell, et al. (1959), respectively. However, it is recognized that the temperature of water consumed by humans is quite obviously variable, and no study will represent the temperature of water consumed by all Americans.

Thus, based on the prevention of undesirable organoleptic qualities, the criteria recommended for 2,3-, 2,5-, 2,6-, and 3,4-dichlorophenols are 0.04 µg/l, 0.5 µg/l, 0.2 µg/l, and 0.3 µg/l, respectively. It is emphasized that these are criteria based on aesthetic rather than health effects. Data on human health effects must be developed as a more substantial basis for recommending a criterion for the protection of human health.

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TRICHLOROPHENOLS

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Trichlorophenols are used as antiseptics and disinfectants, as well as being intermediates in the formation of other chemical products. The most widely recognized of a number of possible isomers is 2,4,5-trichlorophenol. Other isomers include: 3,4,5-, 2,4,6-, 2,3,4-, 2,3,5-, and 2,3,6-trichlorophenols. The physiochemical properties of these isomers are listed in Table 1.

In the evaluation of the trichlorophenols there is a related contaminant that is the subject of separate consideration by regulatory agencies, including the U.S. EPA. A major use of 2,4,5-trichlorophenol is as a feedstock in the synthesis of various pesticides, including the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), Silvex®, Erbon®, and the insecticide Ronnel®. All of these products involve 2,4,5-trichlorophenol in their manufacturing processes and may contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This highly toxic contaminant caused the U.S. EPA to publish a Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing 2,4,5-T (43 FR 17116). The published RPAR indicated that 2,4,5-trichlorophenol is also the subject of a separate potential RPAR.

TCDD is a known teratogen (Courtney, 1976) and carcinogen (Van Miller, et al. 1978). Its extreme toxicity is not disputed. The water solubility of TCDD is 0.2 µg/l. TCDD is produced during the formation of 2,4,5-trichlorophenol. Most documented cases of adverse health effects have involved industrial accidents where

TABLE 1

Physiochemical Properties of Trichlorophenols*

Properties	Trichlorophenol Isomers			
	2,3,4-	2,3,5-	2,3,6-	2,4,5-
Moleclar Weight	197.45	197.45	197.45	197.45
Formula	C_6H3Cl_3O	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$
Melting point °C	83.5	62	58	68-70
Boiling point °C	sublimes	248.5	--	sublimes
Solubility				
water	--	slightly	slightly	slightly
alcohol	soluble	soluble	very	soluble
ether	soluble	soluble	very	--
benzene	soluble	--	very	--
Vapor pressure	--	--	--	1 mm Hg, 72°C
CAS Number	--	--	933-75-5	95-95-4

TABLE 1 (Continued)

Properties	Trichlorophenol Isomers	
	2,4,6-	3,4,5-
Molecular weight	197.5	197.5
Formula	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$
Melting point °C	69.5	101
Boiling point °C	246	271-7
Density	1.490	--
Solubility		
water	slightly	slightly
alcholol	soluble	--
ether	soluble	soluble
Vapor pressure	1 mm Hg, 76°	--
CAS Number	88-06-2	609-19-8

*Weast (ed.), 1978

exothermic reactions resulted in explosions and exposure of humans and the environment. Whiteside (1977) described a 1949 explosion of a 2,4,5-T process that resulted in 228 cases of chloracne. Chloracne is generally recognized as one of the outward and early symptoms of TCDD toxicosis. Others have reported chloracne in employees in 2,4-D and 2,4,5-T plants (Bleiberg, et al. 1964). The 1976 explosion in Seveso, Italy in which 1 to 5 kg of TCDD were released has received much attention.

A complete assessment of the toxicity of TCDD in trichlorophenol-derived chemicals is beyond the scope of this document. The RPAR published in the Federal Register presents the critical studies for evaluation. No tolerance level has yet been established for TCDD.

Crosby and Wong (1973) found that 2,4,5-trichlorophenol is a photodecomposition product of the herbicide 2,4,5-T. About 38 percent of the 2,4,5-T was converted to the trichlorophenol.

EXPOSURE

Ingestion from Water

Piet and DeGrunt (1975) found unspecified trichlorophenol isomers in surface waters in The Netherlands, at concentrations from 0.003 to 0.1 μg/l (ppb).

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to result in water concentrations of 300 to 960 μg/l. Phenols are found in raw domestic sewage at levels of 70 to 100 μg/l. Complex phenols are at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

The association of unpleasant taste or odor of tap water with chlorophenols has been of interest for a number of years (Hoak, 1957; Burttschell, et al. 1959; Campbell, et al. 1958). Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2 to 0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for trichlorophenols in water are shown in Table 2. Table 3 contains a summary of taste threshold data for the trichlorophenols in water.

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme, 2- and 4-chlorophenols are formed early. These molecules are further chlorinated to 2,6- or 2,4-dichlorophenol. The final product is 2,4,6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's study consisted of less than 5 percent each 2- and 4-chlorophenol, 25 percent of 2,6-dichlorophenol, 20 percent 2,4-dichlorophenol and 40 to 50 percent 2,4,6-trichlorophenol.

Ingestion from Food

One possible source of trichlorophenol exposure for humans is through the food chain, as a result of the ingestion by grazing

TABLE 2

Odor Thresholds for Trichlorophenols in Water

	Threshold		Reference
	(µg/l)	(°C)	
2,3,6-Trichlorophenol	300	20-22	3
2,4,5-Trichlorophenol	11	25	1
	200	20-22	3
2,4,6-Trichlorophenol	100	30	1
	1,000	25	2
	300	20-22	3

1 - Hoak, 1957
2 - Burttschell, et al. 1959
3 - Dietz and Traud, 1978

TABLE 3

Summary of Taste Threshold Concentrations of Trichlorophenols in Water

Compound	Threshold (μg/l)	Reference
2,3,6-Trichlorophenol	0.5	Deitz and Traud, 1978
2,4,5-Trichlorophenol	1.0	Deitz and Traud, 1978
2,4,6-Trichlorophenol	2.0	Deitz and Traud, 1978

animals of the chlorophenoxy acid herbicides 2,4,5-T (2,4,5-trichlorophenoxy-acid) or Silvex® (2-(2,4,5-trichlorophenoxy) propionic acid). Residues of the herbicides on sprayed forage are estimated to be in the range of 100 to 300 ppm. In view of this, Clark, et al. (1976) fed Silvex® cattle at levels of 300, 1,000, and 2,000 ppm in the diet for 28 days, and fed 2,4,5-T or Silvex® to sheep at 2,000 ppm in the diet for 28 days. Based on feed consumption, the exposures were equivalent to 9 mg/kg (300 ppm), 30 mg/kg (1,000 ppm) and 60 mg/kg (2,000 ppm). Before tissue samples were obtained some animals were fed a clean diet during a 7-day withdrawal. Muscle, fat, liver, and kidney were analyzed for 2,4,5-trichlorophenol. In the sheep fed 2,000 ppm 2,4,5-T and killed at the end of the 28-day feeding period, the 2,4,5-trichlorophenol residues were 0.13 ppm in muscle, less than 0.05 ppm in fat, 6.1 ppm in liver, and 0.9 ppm in kidney. Sheep held for the 7-day withdrawal period had 2,4,5-trichlorophenol residues of 4.4 ppm in liver and 0.81 ppm in kidney, and less than 0.05 ppm in fat and muscle. Levels of the 2,4,5-T herbicide at the end of 28 days ranged from 0.27 ppm in fat to 27 ppm in kidney. In sheep and cattle fed 2,000 ppm of Silvex®, 2,4,5-trichlorophenol was not detected in muscle or fat at the end of 28 days. Residues in the liver were 0.2 to 0.5 ppm and in kidney were 0.1 to 0.17 ppm.

Bjerke, et al. (1972) fed lactating cows 2,4,5-T and analyzed the milk for trichlorophenol. At feeding levels of 100 ppm 2,4,5-T, an occasional residue of 0.06 ppm or less of trichlorophenol was detected. At 1,000 ppm 2,4,5-T in the diet, residues of 0.15 to 0.23 ppm trichlorophenol were found in milk and cream. Three days after 2,4,5-T feeding at the 1,000 ppm level was stopped, trichlorophenol residues in milk and cream were below detection limits of 0.05 ppm. Acid hydrolysis of milk samples indicated that there was no binding of the trichlorophenol.

Wright, et al. (1970) found that sheep metabolize the herbicide Erbon® (2-(2,4,5-trichlorophenoxy)ethyl-2,2-dichloropropionate). Two metabolites were found in urine, 2-(2,4,5-trichlorophenoxy)-ethanol and 2,4,5-trichlorophenol. About 33 percent of the administered Erbon® dose was eliminated as 2,4,5-trichlorophenol in urine in 96 hours. A dose of 100 mg Erbon®/kg in sheep for seven days proved lethal. 2,4,5-Trichlorophenol residues in tissue were 0.21 ppm in brain, 5.54 ppm in kidney, 3.14 ppm in liver, 2.06 ppm in omental fat, and 1.00 ppm in muscle. Dosages of 50 mg Erbon®/kg for 10 days followed by slaughter on day 11 resulted in no detectable 2,4,5-trichlorophenol residues in tissues.

Stannard and Scotter (1977) from New Zealand determined the residues of various chlorophenols in dairy products following the use of chlorophenol-containing dairy teat sprays, dairy soaps, and antiseptics. The compound 3,5-dimethyl-4-chlorophenol was shown to carry over into milk following application to the cow udder. While this particular compound is not of direct interest in this document, the possible mechanism of exposure deserves recognition.

Exposure to other chemicals could result in exposure to trichlorophenols via metabolic degradation of the parent compound. Kohli, et al. (1976) found that the major rabbit urinary metabolites of 1,2,4-trichlorobenzene were 2,4,5- and 2,3,5-trichlorophenol. 1,2,3-trichlorobenzene was metabolized to 2,3,4-trichlorophenol and smaller amounts of 2,3,6- and 3,4,5-trichlorophenol. 1,3,5-trichlorobenzene was metabolized to 2,3,5- and 2,4,6-trichlorophenol. The yields of metabolites ranged from 1 to 11 percent. Foster and Saha (1978) reported that chicken liver homogenates would metabolize lindane and the alpha and delta but not the beta isomers of 1,2,3,4,5,6-hexachlorocyclohexane. The metabolic products included 2,4,6-trichlorophenol, and 2,3-dichlorophenol, as well as di- and trichlorobenzenes. Tanaka, et al. (1977) found that isolated rat liver microsomes metabolized the alpha, beta, gamma, delta, and epsilon isomers of hexachlorocyclohexane to 2,4,6-trichlorophenol.

Shafik, et al. (1972) showed that in 1 to 2 days, 30 to 50 percent of the insecticide Ronnel® (0,0-dimethyl-0-(2,4,5-trichlorophenyl)phosphorothioate) was excreted in the urine of rats as 2,4,5-trichlorophenol.

Even plants can metabolize another chemical to form a trichlorophenol metabolite. Moza, et al. (1974) demonstrated that corn and pea plants could metabolize pentachlorocyclohexene to the 2,4,6-, 2,3,5-, and 3,4,6-trichlorophenol isomers.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state BCF is available for trichlorophenols, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the steady-state BCF for aquatic organisms that contain about 7.6 percent lipids from the octanol-water partition coefficient (P). Measured log P values were obtained from Hansch and Leo (1979). An adjustment factor of 3.0/7.6 = 0.0395 is used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCF for the edible portion of all aquatic organisms consumed by Americans can be calculated.

Compound	Log P Meas.	Log P Calc.	BCF	Weighted BCF
2,4,5-trichlorophenol	3.72		290	110
2,4,6-trichlorophenol	3.87		389	150

Inhalation

No quantitative data on inhalation studies were found. From Table 1 it is noted that the vapor pressures of 2,4,5- and 2,4,6-trichlorophenol are about 1 mmHg at 72 to 76°C. Consequently the trichlorophenols can be expected to vaporize to some extent.

Olie, et al. (1977) reported finding di-, tri- and tetrachlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

Roberts, et al. (1977) used human epidermal membranes obtained at autopsy in an *in vitro* test system to determine the permeability of human skin to various chemicals. 2,4,6-Trichlorophenol permeated the skin membrane and did not cause damage when tested at the maximum aqueous solubility of 0.09 percent (w/v) concentration.

PHARMACOKINETICS

Absorption, Distribution, and Metabolism

Chlorophenols as a chemical class tend to be rapidly eliminated in the urine. Hence, analyzing urine for trichlorophenol residues is a reasonable approach to estimating exposure, regardless of the source and route of exposure. Dougherty and Piotrowska (1976) used negative chemical ionization mass spectrometry to analyze urine samples for chlorophenols. Evidence was obtained suggesting the presence of trichlorophenol or trichlorophenoxy herbicides in 9 to 67 percent of the 57 samples analyzed. The concentrations were not quantified.

Kutz, et al. (1978) analyzed 418 samples of human urine collected from the general population via the Health and Nutritional

Examination Survey. Residues of 2,4,5-trichlorophenol were found in 1.7 percent of the samples. The average level found was less than 5 μg/l (ppb) and the maximum value found was 32.4 μg/l.

Excretion

2,4,5-Trichlorophenol is cleared rapidly from blood. Wright, et al. (1970) dosed sheep with Erbon®, a herbicide that is metabolized to 2,4,5-trichlorophenol, and observed the disappearance of 2,4,5-trichlorophenol from the blood. An approximate blood half-life of 20 hours was estimated from the graphed data.

Another study showed the rapid clearance of 2,4,6-trichlorophenol, predominantly in urine. Korte, et al. (1978) administered 1 ppm 2,4,6-trichlorophenol in the diet to rats for three days and then studied elimination. Eighty-two percent of the dose was eliminated in the urine and 22 percent in the feces. Radio-labeled trichlorophenol was not detected in liver, lung or fat obtained five days after the last dose.

EFFECTS

Acute, Subacute, and Chronic Toxicology

Table 4 presents data regarding acute toxicity of several trichlorophenol isomers. Differences in observed LD_{50} values may be due to the use of different solvents.

The clinical signs of acute poisoning with 2,4,5-trichlorophenol include decreased activity and motor weakness (Deichmann, 1943). Convulsive seizures also occur, but are not as severe as with the monochlorophenols, which at physiological pH (7.0 to 7.4), are mainly undissociated. The tri- and tetrachlorophenols have lower pk_a values and, hence, are more extensively dissociated at

TABLE 4

Acute Toxicity of Trichlorophenols

Chemical	Solvent	Species	Toxic Response	Reference
2,4,5-Trichlorophenol	Fuel oil	Rat	Oral LD_{50} = 820 mg/kg	Deichmann & Mergard, 1948
	Corn oil	Rat	Oral LD_{30} = 2,960 mg/kg	McCollister, et al. 1961
	Fuel oil	Rat	Subcutaneous LD_{50} = 2,260 mg/kg	Deichman & Mergard, 1948
	Olive oil	Rat	Intraperitoneal LD_{50} = 355 mg/kg	Farquharson, et al. 1958
3,4,5-Trichlorophenol	Olive oil	Rat	Intraperitoneal LD_{50} = 372 mg/kg	Farquharson, et al. 1958
2,4,6-Trichlorophenol	Olive oil	Rat	Intraperitoneal LD_{50} = 276 mg/kg	Farquharson, et al. 1958
2,3,6-Trichlorophenol	Olive oil	Rat	Intraperitoneal LD_{50} = 308 mg/kg	Farquharson, et al. 1958

physiological pH. These compounds, with the exception of 2,4,6-trichlorophenol tend not to be convulsants.

Farquharson, et al. (1958) determined LD_{50} values of isomers of trichlorophenol (Table 4). 2,4,6-Trichlorophenol produced convulsions when injected intraperitoneally. The 2,3,6-isomer occasionally caused convulsions when dosed animals were handled. All of the trichlorophenol isomers (3,4,5-, 2,4,5-, 2,4,6-, and 2,3,6-) elevated body temperature by $0.5^{\circ}C$. Onset of rigor mortis occurred within five minutes of death as compared to 50 minutes for controls. Rats dosed with 2,3,6-, 3,4,5-, or 2,4,5-trichlorophenol developed hypotonia in the hind limbs 2 to 3 minutes after intraperitoneal injection. The hypotonia then spread to the forelimbs and neck. All of the trichlorophenol isomers stimulated oxygen consumption of rat brain homogenate at concentrations of 5×10^{-5} to 10^{-3}M.

McCollister, et al. (1961) conducted a variety of toxicologic studies on 2,4,5-trichlorophenol in rats. The 2,4,5-trichlorophenol used in the acute studies was 97 to 98 percent pure; and, for the 90-day study, it was 99 percent pure. The acute oral LD_{50} was 2,960 mg/kg.

Rabbits were given 28 daily oral doses of 2,4,5-trichlorophenol in 5 percent gum acacia solution (McCollister, et al. 1961). No effect was observed at doses of 1 or 10 mg/kg. At 100 mg/kg, slight renal pathology was reported. At 500 mg/kg, slight kidney and liver lesions were noted.

In rats, 18 daily doses of 1,000 mg/kg during 24 days caused a transient weight loss that disappeared within 14 days (McCollister, et al. 1961). Dosages of 30, 100, 300, or 1,000 mg/kg for 18 of 24 days did not affect mortality, hematological variables (unspecified), blood urea nitrogen, final body weight, or organ weight ratios. There were no microscopic lesions in lung, heart, liver, kidney, spleen, adrenal, pancreas or testes.

Rats in groups of 10 males and 10 females were fed 2,4,5-trichlorophenol at dietary levels of 100, 300, 1,000, 3,000, or 10,000 mg of compound per kg of feed for 98 days (McCollister, et al. 1961). Assuming that an average rat consumes an amount of feed equivalent to 10 percent of its body weight daily, the equivalent doses were 10, 30, 100, 300, and 1,000 mg/kg body weight.

Dosages of 100 mg/kg body weight or less produced no adverse effects as judged by behavior, mortality, food consumption, growth, terminal hematology, body and organ weights, and gross and microscopic pathology.

At 1,000 mg/kg (10,000 mg/kg in diet), growth was slowed in fe males. There were no significant hematologic changes. Changes were noted in kidney and liver on histopathologic examination. The kidneys showed moderate degenerative changes in the convoluted tubular epithelium and early proliferation of interstitial tissue. The liver showed mild centrilobular degenerative changes characterized by cloudy swelling and occasional focal necrosis. There was slight proliferation of the bile ducts and early portal cirrhosis. The rats fed 300 mg/kg (3,000 mg/kg feed) also showed histopathologic changes in kidney and liver that were milder than those observed in the higher dose. The histopathologic changes were considered to be reversible.

Anderson, et al. (1949) fed steers various levels of 2,4,5-trichlorphenyl acetate or zinc 2,4,5-trichlorophenate, as shown in Table 5. Feed consumption, daily weight gain, hemoglobin, and packed cell volume were determined. The results are summarized in Table 6. Because of the limited number of animals per group, statistical analysis was not done. Additionally, for day 154, there was only one control animal per compound. The authors concluded that the compounds were relatively nontoxic to the animals. Examination of Table 6 shows no clinically significant changes in hemoglobin or packed cell volume values. No gross lesions were observed at slaughter. The feed consumption data suggest that with both compounds, the high dose groups were consuming less feed/kg/day. Tissues were not analyzed for the active agents. Tissue analyses showed an increase in zinc, but phenol was not detected. Meat prepared from the animals did not have any unusual taste or odor.

McCollister, et al. (1961) reported on skin irritation and sensitization studies in 200 humans. A 5 percent solution of 2,4,5-trichlorophenol in sesame oil was mildly irritating in a few individuals upon prolonged contact, but there was no evidence of sensitization.

Bleiberg, et al. (1964) described various adverse health effects in 29 workers involved in the manufacture of 2,4-D and 2,4,5-T. The workers had varying degrees of chloracne, hyperpigmentation, and hirsutism. Eleven had elevated urinary uroporphyrins. Eleven of the 29 were diagnosed as having evidence of

Table 5

Steer Feeding Study Design*

Group	N	Compound	Dose-mg/kg	Duration-days
1	2	zinc 2,4,5 trichlorophenate	0	---
2	2	"	17.64	78
3	2	"	52.92	154
4	2	"	158.77	78
5	2	2,4,5-trichlorophenyl acetate	0	---
6	2	"	17.64	78
7	2	"	52.92	154
8	2	"	158.77	78

*Anderson, et al. 1949
N - Number of animals tested

Table 6

Average Results of Trichlorophenol Steer Feeding Study*

Part 1: Results of feeding zinc 2,4,5-trichlorophenate

	Dose - mg/kg			
	0	17.64	52.92	158.77
Daily gain - 78 day (kg/day)	0.73	0.97	0.83	0.68
Daily gain - 154 day (kg/day)	0.77	--	0.71	--
Feed consumption				
(gm/kg/day) 1- 78 day	35	32	33	24
(gm/kg/day) 1-154 day	30	--	37	--
Hemoglobin				
(gm/100 ml) 78 day	10.3	11.1	10.3	10.9
(gm/100 ml) 154 day	10.9	--	10.4	--
Packed cell volume				
PCV - 78 day	34	37	34	37
PCV - 154 day	36	--	35	--

TABLE 6 (Continued)

Part 2: Results of feeding 2,4,5-trichlorophenyl acetate				
	Dose - mg/kg			
	0	17.64	52.92	158.77
Daily gain				
(kg/day) 78 day	1.05	0.37	0.84	0.65
Daily gain				
(kg/day) 154 day	0.77	--	0.68	--
Feed consumption				
(gm/kg/day) 1- 78 day	36	37	37	30
(gm/kg/day) 1-154 day	30	--	39	--
Hemoglobin				
(gm/100 ml) 78 day	9.1	12.1	11.1	11.7
(gm/100 ml) 154 day	--	--	11.3	--
Packed cell volume				
PCV - 154 day	31	40	37	38
PCV - 154 day	--	--	38	--

*Source: Anderson, et al. 1949

porphyria cutanea tarda, which is associated with liver dysfunction, porphyrinuria, and bullous skin lesions. It is likely that some of these symptoms represent TCDD toxicosis.

Studies on the mechanism of action or subcellular effects of these compounds have primarily focused on effects on oxidative phosphorylation. Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation in vitro. 2,4,5-Trichlorophenol caused complete uncoupling at 0.05 mM. The known uncoupler 2,4-dinitrophenol completely uncoupled the test system at 0.1 mM for comparison. There was a positive relationship between mitochondria protein binding and uncoupling properties.

Parker (1958) studied the effect of chlorophenols on isolated rat liver mitochondria. 2,4-Dinitrophenol was used as a reference compound because of its known ability to uncouple oxidative phosphorylation. An unspecified isomer of trichlorophenol, at 1.8×10^{-4}M, had 70 percent of the activity of 2,4-dinitrophenol at 2.0×10^{-5}M. Mitsuda, et al. (1963) studied the effects of various chlorophenols on oxidative phosphorylation in isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, with 0.05 ml of mitochondrial suspension containing 0.43 mg N. The concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP was determined (I_{50}). The I_{50} was 3 μM for 2,4,5-trichlorophenol and 18 μM for 2,4,6-trichlorophenol.

Stockdale and Selwyn (1971) reported that 2,4,6-trichlorophenol at 0.005 M resulted in 50 percent inhibition of lactate dehydrogenase, and that 0.0028 M resulted in 50 percent inhibition of hexokinase in vitro. Isolated ATPase was stimulated by 60 μM and inhibited by 1,120 μM 2,4,6-trichlorophenol.

Arrhenius, et al. (1977) studied the effects of chlorophenols on microsomal detoxication mechanisms using rat liver preparations. The experimental system examined the effects of each tested chlorophenol on the microsomal metabolism of N, N-dimethylaniline (DMA) to formaldehyde and N-methylaniline (C-oxygenation) or to N, N-dimethylaniline-N-oxide (N-oxygenation). In essence, the study examined disturbances in the detoxification electron transport chain. The concern as stated by Arrhenius, et al. (1977) was that compounds that could increase N-oxygenation could also influence the metabolism of other chemical toxicants, such as aromatic amines, which are formed by N-oxygenation. It was suggested that agents which increase N-oxygenation could be considered as synergists for the carcinogenic action of aromatic amines. A concentration greater than 1 mM of 2,4,6-trichlorophenol inhibits C-oxygenation of DMA. A 3 mM concentration produces a small increase in N-oxygenation of DMA. In order to set this in a dose-response context, a concentration of 1 mM is equivalent to 197.46 mg trichlorophenol per liter and 3 mM is equivalent to 592.38 mg/l.

Two studies have examined the effect of trichlorophenol on the biochemistry of the lens of the eye. Korte, et al. (1976) showed that 10^{-3} M 2,4,5-trichlorophenol would reduce the bovine lens content of ATP, ADP, glucose-6-phosphate and fructose following a 48-hour incubation. Levels of AMP and glucose were increased. Trichlorophenol decreased glucose-6-phosphate dehydrogenase activity but had no effect on lactate dehydrogenase, malate dehydrogenase, sorbitol dehydrogenase, fructose-1,6-diphosphate aldolase, or pyruvate kinase. Ismail, et al. (1975) showed that small amounts of 2,4,6-trichlorophenol would penetrate the rabbit eye. Small amounts of the chemical were placed in the eye and one hour later various parts of the eye were analyzed for the chemical. Highest amounts of the administered dose were found in the cornea (2.4 percent) and conjunctiva (2.49 percent). The aqueous and vitreous humor, lens, iris, and choroid contained less than 0.17 percent each.

Synergism and/or Antagonism and Teratogenicity

Pertinent data could not be located in the available literature.

Mutagenicity

Fahrig, et al. (1978) found that 400 mg 2,4,6-trichlorophenol increased the mutation rate in a strain of *Saccharomyces cerevisiae*. There was no effect on the rate of intragenic recombination.

In a mouse spot test, females were administered an intraperitoneal dose of test chemical on day 10 of gestation; the response was a change in hair coat color representing a genetic change in the offspring (Fahrig, et al. 1978). At 50 mg/kg, 2,4,6-trichlorophenol produced two spots in 2 of 340 animals from 74 females. At 100 mg/kg, there was one spot in 175 mice from 42 females.

Rasanen, et al. (1977) tested chlorophenol for mutagenicity using the *Salmonella*-mammalian microsome Ames test with both the nonactivated and activated systems. The following trichlorophenol isomers were tested and reported as non-mutagenic in both test systems: 2,3,5-, 2,3,6-, 2,4,5-, and 2,4,6-trichlorophenol.

Carcinogenicity

Boutwell and Bosch (1959) conducted a series of experiments on the tumor promoting action of substituted phenols using repeated applications of concentrated solutions to the shaved backs of mice. The tumor initiator DMBA (9,10-dimethyl-1,2-benzanthracene) was used. A 20 percent solution of 2,4,6-trichlorophenol in benzene did not increase the incidence of papillomas in mice pretreated with DMBA. No carcinomas developed during the 15-week experiment. A 21 percent solution of 2,4,5-trichlorophenol in acetone increased the incidence of papillomas in mice pretreated with DMBA. Carcinomas did not develop during the 16-week experiment.

Innes, et al. (1969) dosed two strains of mice with 2,4,6-trichlorophenol for 18 months. Eighteen males and 18 females of each strain were used, for a total of 72 animals. Beginning at seven days of age and continuing through 28 days, the mice were gavaged daily with the compound at 100 mg/kg. From 1 to 18 months the mice were fed a diet containing 260 ppm, which resulted in an estimated exposure of 20 to 25 mg/kg. The results were inconclusive. In this study, which involved 120 pesticides, each chemical was grouped into 1 of 3 categories. If the incidence of tumors was significantly increased, it was classified as a carcinogen. If the incidence of tumors was low and statistically insignificant, it was classified as a noncarcinogen. The third category, in which 2,4,6-trichlorophenol was placed, comprised compounds requiring further study. The authors did not provide the actual data, but indicated that there was an elevation of tumor incidence in an uncertain range, and that additional statistical evaluation or experimentation would be required before an interpretation could be made.

A bioassay of 2,4,6-trichlorophenol for possible carcinogenicity was conducted for the National Cancer Institute (NCI) by Litton Bionetics, Inc. The test chemical was administered in feed to groups of F344 rats and B6C3F$_1$ mice using standard NCI protocols (Table 7 and Table 8).

The mean body weights of dosed rats and mice of each sex showed a dose-related decrease when compared to the corresponding controls. However, the dose-related trends in mortality were not observed in rats or mice; nor were other clinical signs of toxicity found.

The significant positive effects of dietary 2,4,6-trichlorophenol on tumor incidence in male rats, male mice, and female mice are summarized in Table 9 and Table 10. In male rats, increases in lymphoma or leukemia were dose-related (4/20 controls, 25/50 low dose, 29/50 high dose). However, in female rats, the incidence of these tumors was not significantly elevated. Leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow occurred in both male and female rats. In both the male and female mice, the incidence of hepatocellular carcinomas or adenomas was increased significantly over the controls and was also dose-related (males: controls 4/20, low dose 32/49, high dose 39/47; females: controls 1/20, low dose 12/50, high dose 24/48).

Based on the results of this study, the National Cancer Institute concluded that 2,4,6-trichlorophenol was carcinogenic in male

TABLE 7

2,4,6-Trichlorophenol Chronic Feeding Studies in Rats[a]

Sex and Test Group	Initial No. of Animals[b]	2,4,6-Trichlorophenol in Diet[c] (ppm)	Time on Study (Weeks)
Male			
Matched-control	20	0	107
Low-dose	50	5,000	106
High-dose	50	10,000	106
Female			
Matched-control	20	0	107
Low-dose	50	5,000	106-107
High-dose	50	10,000	106

[a] National Cancer Institute, 1979
[b] All animals were 6 weeks of age when placed on study
[c] Test and control diets were provided *ad libitum* 7 days per week

TABLE 8

2,4,6-Trichlorophenol Chronic Feeding Studies in Mice[a]

Sex and Test Group	Initial No. of Animals[b]	2,4,6-Trichlorophenol in Diet[c] (ppm)	Time on Study (Weeks)	Time-Weighted Average Dose (ppm)[d]
Male				
Matched-control	20	0	105	
Low-dose	50	5,000	105	
High-dose	50	10,000	105	
Female				
Matched-control	20	0	105	
Low-dose	50	10,000 2,500	38 67	5,214
High-dose	50	20,000 5,000	38 67	10,428

[a] National Cancer Institute, 1979

[b] All animals were 6 weeks of age when placed on study

[c] Test and control diets were provided *ad libitum* 7 days per week

[d] Time-weighted average dose = $\frac{\Sigma\,(\text{dose in ppm x no. of weeks at that dose})}{\Sigma\,(\text{no. of weeks receiving each dose})}$

TABLE 9

Analysis of the Incidence of Lymphoma or Leukemia in F344 Rats Administered 2,4,6-Trichlorophenol in the Diet*

Sex	Matched Control	Low-Dose	High-Dose
Female	3/20 (15)[a]	11/50 (22)	13/50 (26)
	N.S.[b]	N.S.	N.S.
	103[c]	69	55
Male	4/20 (20)	25/50 (50)	29/50 (58)
	P = 0.006	P = 0.019	P = 0.004
	107	64	69

*Source: Modified from the National Cancer Institute, 1979

[a] Number of tumor-bearing animals/number of animals examined at site (percent)

[b] Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dose group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated

[c] Time to first tumor (weeks)

TABLE 10

Analysis of the Incidence of Hepatocellular Carcinoma or Adenoma in $B6C3F^1$ Mice Administered 2,4,6-Trichlorophenol in the Diet*

Sex	Matched Control	Low-Dose	High-Dose
Female	1/20 (5)[a]	12/50 (24)	24/48 (50)
	P less than 0.001[b]	N.S.	P less than 0.001
	105[c]	105	105
Male	4/20 (20)	32/49 (65)	39/47 (83)
	P less than 0.001	P = 0.001	P less than 0.001
	97	102	95

*Source: Modified from the National Cancer Institute, 1979

[a] Number of tumor-bearing animals/number of animals examined at site (percent)

[b] Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated

[c] Time to first tumor (weeks)

F344 rats (including lymphomas or leukemias), and was also carcinogenic in both sexes of $B6C3F_1$ mice (inducing hepatocellular carcinomas or adenomas).

CRITERION FORMULATION

Existing Guidelines and Standards

Existing standards were not found for the trichlorophenols in the available literature.

Current Levels of Exposure

Pertinent data could not be located in the available literature concerning current levels of exposure to the trichlorophenols.

Special Groups at Risk

No special group has been identified as being at increased risk of exposure to the trichlorophenols.

Basis and Derivation of Criteria

The only trichlorophenol isomer for which adequate data exists for calculation of a toxicity based criterion is 2,4,5-trichlorophenol. McCollister, et al. (1961), in a 98-day feeding study on rats, demonstrated the no-observed-effect level (NOEL) for 2,4,5-trichlorophenol to be 100 mg/kg. Using the National Academy of Sciences (1977) recommended uncertainly factor of 1,000, assuming an average human body weight of 70 kg, an allowable daily intake (ADI) can be calculated, as follows:

$$\text{ADI} = \frac{100\ \text{mg/kg}}{70\ \text{kg} \times 1,000} = 7\ \text{mg}$$

For the purpose of establishing water quality criteria, it is assumed that on the average, a person ingests 2 liters of water per day and 6.5 grams of fish. Since fish may bioaccumulate substances, a BCF is used on the calculation. The BCF for 2,4,5-trichlorophenol is 110. The acceptable concentration of 2,4,5-trichlorophenol in water is calculated, as follows:

$$C = \frac{\text{ADI}}{2\ l + (0.0065 \times F)}$$

$$C = \frac{7\ \text{mg}}{2 + (0.0065 \times 110)}$$

$$C = 2.58\ \text{mg/l}\ (\sim\text{or}\ 2.6\ \text{mg/l})$$

where:

2 l = 2 liters of drinking water

0.0065 kg = amount of fish consumed daily

F = bioconcentration factor = 110

ADI = Acceptable Daily Intake (mg/kg for a 70 kg person)

This criterion can alternatively be expressed as 9.8 mg/l if exposure is assumed to be from the consumption of fish and shellfish alone.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities". 2,4,6-Trichlorophenol is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of 2,4,6-trichlorophenol in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of 2,4,6-trichlorophenol corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth. In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the table following.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams fish and shellfish (2)	0.12 µg/l	1.2 µg/l	12 µg/l
Consumption of fish and shellfish only.	0.36 µg/l	3.6 µg/l	36 µg/l

(1) Calculated by applying a linearized multistage model, as described in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document to the animal bioassay data presented in the Appendix and Table 9. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Thirty-three percent of the 2,4,6-trichlorophenol exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 150-fold. The remaining 67 percent of 2,4,6-trichlorophenol exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of 2,4,6-trichlorophenol, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding 2,4,6-trichlorophenol concentrations and, (2) occcurring solely from consumption of aquatic life grown in the waters containing the corresponding 2,4,6-trichlorophenol concentrations. Because data indicating other sources of 2,4,5-trichlorophenol exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

The data of Hoak (1957), Burttschell, et al. (1959), and Dietz and Traud (1978) indicate that 2,4,5- and 2,4,6-trichlorophenol impart disernable organoleptic characteristics to water. (These studies have been discussed previously in the section of this document dealing with monochlorophenols.) The organoleptic detection thresholds for the trichlorophenols are presented in Tables 2 and 3 for odor and taste, respectively.

Since the organoleptic detection threshold concentrations for 2,4,5- and 2,4,6-trichlorophenol are well below any toxicity-based criterion levels that may be derived, the ambient water quality criteria are based on organoleptic data. It should be emphasized that these criteria are based on aesthetic qualities rather than health effects. However, to the extent that these criteria are below the levels derived for 2,4,5-trichlorophenol and 2,4,6-trichlorophenol from toxicity and carcinogenicity data, respectively, they are likely to also be protective of human health.

The taste thresholds determined by Dietz and Traud (1978) for the detection of 2,4,5-trichlorophenol and 2,4,6-trichlorophenol in water are used as the bases for the ambient water quality criteria. The Dietz and Traud study was chosen for a number of reasons. These authors present a recent study involving well-defined procedures and a number of documented controls. This study utilized "fresh" water from the base outlet of the Verse Dam (Germany) for all experiments. The water was described as clear and neutral with respect to both odor and taste. These conditions are considered to more closely approximate the conditions of ambient water found in lakes, rivers, and streams than would those of the Hoak (1957) and Burttschell, et al. (1959) studies, which utilized carbon-filtered laboratory distilled water. The 20 to 22°C temperature of the water in the Dietz and Traud odor and taste tests might also more closely approximate the temperature at which water is normally consumed than do the 30°C or 25°C temperatures used in the studies of Hoak (1957) and Burttschell, et al. (1959), respectively. However, it is recognized that the temperature of water consumed by humans is quite obviously variable, and no study will represent the temperature of water consumed by all Americans.

Therefore, based on the prevention of undesirable organoleptic qualities, the criterion levels for 2,4,5- and 2,4,6-trichlorophenol in water are 1.0 μg/l and 2.0 μg/l, respectively. These levels should be low enough to prevent detection of objectionable organoleptic characteristics and far below minimal no-effect concentrations determined in laboratory animals.

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TETRACHLOROPHENOL

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Tetrachlorophenol is a fungicide and wood preservative. As either a spray or dip treatment, it is used as a water soluble salt to treat freshly cut lumber. The treatment prevents sap stain organisms from growing in wood while it is drying or waiting further processing.

Commercial pentachlorophenol contains 3 to 10 percent tetrachlorophenol (Goldstein, et al. 1977; Schwetz, et al. 1978). Since the annual production of pentachlorophenol is 25 million kg, 0.75 to 2.5 million kg of tetrachlorophenol are produced concurrently.

There are three tetrachlorophenol isomers the most important of which is 2,3,4,6-tetrachlorophenol. Table 1 lists the physiochemical properties of the three isomers.

Like tri- and pentachlorophenols, tetrachlorophenols contain toxic nonphenolic impurities. Schwetz, et al. (1974) reported that commercial grade 2,3,4,6-tetrachlorophenol contained chlorodioxin isomers at levels of 28 ppm (hexa-), 80 ppm (hepta-), and 30 ppm (octachlorodibenzo-p-dioxin) as well as chlorodibenzofurans at levels of 55 ppm (hexa-), 100 ppm (hepta-), and 25 ppm (octachlorodibenzofuran). The commercial tetrachlorophenol was composed of 73 percent tetra- and 27 percent pentachlorophenol.

EXPOSURE

Ingestion from Water

There are reports suggesting the presence of lower chlorophenols occurring in drinking water, but the presence of

TABLE 1

Physiochemical Properties of Tetrachlorophenol*

Property	Tetrachlorophenol Isomer		
	2,3,4,5-	2,3,4,6-	2,3,5,6-
Molecular weight	231.89	231.89	231.89
Formula	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$
Melting point °C	116-7	70	115
Boiling point °C	sublimes	sublimes	150
Solubility			
water	-	slightly	slightly
alcohol	very	soluble	-
benzene	-	soluble	very
Vapor pressure	1mm Hg, 100°C	-	-
CAS Number		58-90-2	935-95-5

*Source: Weast, (ed.), 1978

tetrachlorophenol has not been documented. The odor threshold for 2,3,4,6-tetrachlorophenol has been reported by Hoak (1957) to be 915 µg/l at 30°C and by Deitz and Traud (1978) to be 600 µg/l. The taste threshold of 1 µg/l for 2,3,4,6-tetrachlorophenol in water has been reported by Deitz and Traud (1978). These studies are described in the monochlorophenols portion of this document (see Ingestion from Water).

Ingestion from Food

There is no evidence to suggest that tetrachlorophenols may be ingested from foods. If such compounds were present in foods, they could probably be absorbed from the gut.

One interesting problem associated with exposure of poultry to tetrachlorophenol-treated wood shavings has been the resulting musty taint that develops in meat and eggs. Parr, et al. (1974) conducted a small survey on the amount of tetra- and pentachlorophenol entering poultry housing as a result of using treated wood shavings. The problem developed when a musty taint was observed in broiler chickens. The musty taint was due to the fungal formation of tetra-and pentachloroanisoles formed by the methylation of the parent chlorophenol. The average 2,3,4,6-tetrachlorophenol concentration in fresh shavings was 54 µg/g (ppm). The spent litter contained 0.7 µg/g tetrachlorophenol and 0.5 µg/g tetrachloroanisole. The tetrachloroanisole was only occasionally detected in fresh shavings. The odor threshold for 2,3,4,6-tetrachloroanisole was reported to be 4 x 10^{-6} µg/g (4 ppt).

Harper and Balnove (1975) analyzed tissues from chickens raised in contact with tetrachlorophenol-treated wood shavings.

The levels of tetrachloroanisole in the chickens ranged from 1.2 ng/g in the edible portion to 7.6 ng/g in bone.

Engel, et al. (1966) fed 1 mg of 2,3,4,6-tetrachloroanisole/kg to chickens. A musty taint developed in eggs and broiler meat similar to that associated with housing chickens over tetrachlorophenol-treated wood shavings.

There is a possibility that the metabolism of other compounds could result in the formation of tetrachlorophenols. Engst, et al. (1976) reported that rats partially metabolized pentachlorophenol to 2,3,4,6- and 2,3,5,6-tetrachlorophenols. Ahlborg (1978) could not replicate the Engst results but rather found that rats metabolized pentachlorophenol to 2,3,5,6-tetrachlorohydroquinone and trichlorohydroquinone.

Kohli, et al. (1976) studied the metabolism of tetrachlorobenzene in rabbits. 1,2,3,4- and 1,2,3,5-Tetrachlorobenzenes were metabolized to 2,3,4,5- and 2,3,4,6-tetrachlorophenols, respectively. In addition, 1,2,3,5-tetrachlorobenzene resulted in 2,3,4,6-tetrachlorophenol. 1,2,4,5-Tetrachlorobenzene resulted in only one metabolite, 2,3,5,6-tetrachlorophenol. All metabolites were isolated from urine.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportinal to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state BCF is available for any tetrachlorophenols, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the steady-state BCF for aquatic organisms that contain about 7.6 percent lipids from the octanol/water partition coefficient (P). A measured log P value of 4.10 was obtained from Hansch and Leo (1979). The adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCF for the edible portion of all aquatic organisms consumed by Americans can be calculated.

Compound	Log P	BCF	Weighted BCF
2,3,4,6-tetrachlorophenol	4.10	610	240

Inhalation

Olie, et al. (1977) reported finding di-, tri-, and tetrachlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

Pertinent data could not be located in the available literature.

PHARMACOKINETICS

Absorption and Distribution

Pertinent data could not be located in the available literature.

Metabolism and Excretion

Ahlborg and Larsson (1978) studied the urinary metabolites of tetrachlorophenol in rats following intraperitoneal doses of 10 mg/kg. 2,3,5,6-Tetrachlorophenol was excreted as unchanged tetrachlorophenol and as tetrachloro-p-hydroquinone. No trichloro-p-hydroquinone was found in the urine of rats given the 2,3,5,6-tetrachlorophenol isomer. In a quantitative study, rats were given 5.3 mg of 2,3,5,6-tetrachlorophenol, and the urine was collected for 24 hours. Over 98 percent of the administered dose was recovered in the urine in 24 hours, indicating an excretion half-life of less than one day. About 66 percent of the chlorophenol was excreted as unchanged 2,3,5,6-tetrachlorophenol and 35 percent was eliminated as tetrachloro-p-hydroquinone. After 24 hours, neither parent compound nor metabolite could be found in the urine. This may indicate a 1 to 2 percent fecal excretion. The 2,3,4,5,- and 2,3,4,6 tetrachlorophenol isomers are not metabolized to any large extent. The 2,3,4,5-isomer is primarily excreted as unchanged chlorophenol with trace amounts of trichloro-p-hydroquinone appearing in the urine. Fifty-one percent of the administered dose was recovered in the urine in 24 hours. During the second 24 hours, an additional 7 percent of the dose appeared in the urine. Altogether, 59 percent of the intraperitoneal dose was recovered in the urine with the disposition of the remainder of the dose not identified.

The 2,3,4,6-tetrachlorophenol isomer is rapidly eliminated in the urine as unchanged chlorophenol. About 94 percent of the intraperitoneal dose was recovered in the urine in 24 hours. Trace amounts of trichloro-p-hydroquinone were found in the urine. In the experiments of Alhborg and Larsson (1978), the urine was boiled in HCl to split any conjugates such as glucuronides.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The acute toxicity of tetrachlorophenol isomers via various routes and in several species is shown in Table 2. Tetrachlorophenol appears to be less acutely toxic orally than pentachlorophenol. In the studies of Ahlborg and Larsson (1978), pentachlorophenol had an oral LD_{50} of 150 mg/kg in mice and 294 mg/kg in gerbils. The comparative tetrachlorophenol LD_{50}s ranged from 533 to 979 mg/kg. This point will be important in setting the criterion.

Tetrachlorophenol toxicosis consists of depressed activity and motor weakness (Deichmann, 1943). Tremors and convulsions do not occur except in extremes.

Ahlborg and Larsson (1978) determined the acute oral and intraperitoneal LD_{50} of three isomers of tetrachlorophenol and

TABLE 2

Acute Toxicity of Tetrachlorophenol and Metabolites*

Chemical	Solvent	Animal	Toxic Response
2,3,4,6-Tetrachlorophenol	propylene glycol	mouse, C57 female	oral LD_{50} = 150 mg/kg
	propylene glycol	gerbil, female	oral LD_{50} = 698 mg/kg
	ethanol	mouse, C57 female	oral LD_{50} = 131 mg/kg
	ethanol	mouse, C57 male	oral LD_{50} = 163 mg/kg
	ethanol	mouse, C57 female	intraperitoneal LD_{50} = 82 mg/kg
	propylene glycol	mouse, C57 female	intraperitoneal LD_{50} = 121 mg/kg
2,3,5,6-Tetrachlorophenol	propylene glycol	mouse, C57 female	Oral LD_{50} = 543 mg/kg
	propylene glycol	gerbil, C57, female	oral LD_{50} = 979 mg/kg
	ethanol	mouse, C57 female	intraperitoneal LD_{50} = 48 mg/kg
	propylene glycol	mouse, C57 female	intraperitoneal LD_{50} = 109 mg/kg

TABLE 2 (Continued)

Chemical	Solvent	Animal	Toxic Response
2,3,5,6-Tetrachlorophenol	ethanol	mouse, C57 female	oral LD_{50} = 109 mg/kg
	ethanol	mouse, C57 male	oral LD_{50} = 89 mg/kg
2,3,4,5-Tetrachlorophenol	propylene glycol	mouse, C57 female	oral LD_{50} = 677 mg/kg
	propylene glycol	gerbil, female	oral LD_{50} = 533 mg/kg
	ethanol	mouse, C57 female	oral LD_{50} = 400 mg/kg
	ethanol	mouse, C57 male	oral LD_{50} = 572 mg/kg
	ethanol	mouse, C57 female	intraperitoneal LD_{50} = 97 mg/kg
	propylene glycol	mouse, C57 female	intraperitoneal LD_{50} = 133 mg/kg
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 female	oral LD_{50} = 500 mg/kg
Tetrachloropyrocatechol	ethanol	mouse, C57 female	oral LD_{50} = 612 mg/kg
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 male	oral LD_{50} = 750 mg/kg
Tetrachloropyrocatechol	ethanol	mouse, C57 male	oral LD_{50} = 750 mg/kg

TABLE 2 (Continued)

Chemical	Solvent	Animal	Toxic Response
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 female	intreaperitoneal LD_{50} = 35 mg/kg
Tetrachloropyrocatechol	ethanol	mouse, C57 female	intraperitoneal LD_{50} = 136 mg/kg
Pentachlorophenol	propylene glycol	mouse, C57 female	oral LD_{50} = 150 mg/kg
	propylene glycol	gerbil, female	oral LD_{50} = 294 mg/kg
	ethanol	mouse, C57 female	oral LD_{50} = 74 mg/kg
	ethanol	mouse, C57 male	oral LD_{50} = 36 mg/kg
	ethanol	mouse, C57 female	intraperitoneal LD_{50} = 32 mg/kg
	propylene glycol	mouse, C57 female	intraperitoneal LD_{50} = 59 mg/kg

*Source: Ahlborg and Larson, 1978

related compounds in mice and gerbils (Table 2). The effect of solvent is shown by the increased toxicity of the chlorophenols when dissolved in ethanol versus propylene glycol.

Ahlborg and Larsson (1978) also determined the acute oral and intraperitoneal toxicity of tetrachloro-p-hydroquinone, which is the major urinary metabolite of 2,3,5,6-tetrachlorophenol in rats. When administered orally, the metabolite was less toxic than any of the three tetrachlorophenol isomers in either male or female mice. However, when the metabolite was administered intraperitoneally in female mice it was more toxic than any of the three tetrachlorophenol isomers, and the LD_{50} was similar to the intraperitoneal LD_{50} of pentachlorophenol (Table 2).

Farquharson, et al. (1958) showed that the intraperitoneal LD_{50} of 2,3,4,6-tetrachlorophenol in rats was 130 mg/kg. Convulsions did not occur, but there was a rapid 4°C rise in body temperature, and rigor mortis occurred within five minutes of death. Brain homogenate oxygen consumption was stimulated in the presence of 2,3,4,6-tetrachlorophenol at 5×10^{-5} M.

Schwetz, et al. (1974) reported that the 10 day maximum tolerated dose for commercial 2,3,4,6-tetrachlorophenol in rats was 30 mg/kg/day. Deaths occurred in groups given 100 or 300 mg/kg/day.

Several investigators have examined the effect of tetrachlorophenol on cellular metabolism. Mitsuda, et al. (1963) studied the effects of various chlorophenols on oxidative phosphorylation in isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, with 0.05 ml of mitochondrial suspension containing 0.43 mg N. The concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP was determined (I_{50}). 2,3,4,6-Tetrachlorophenol had an I_{50} of 2 µM. For comparison, the I_{50} for pentachlorophenol was 1 µM and for 2,4-dinitrophenol the I_{50} was 17 µM.

Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation *in vitro*. There was a positive relationship between mitrochondrial protein binding and uncoupling properties. 2,3,4,6-Tetrachlorophenol caused complete uncoupling at 0.05 mM. For comparison, the known uncoupler 2,4-dinitrophenol completely uncoupled the test system at 0.1 mM.

Arrhenius, et al. (1977) studied the effects of chlorophenols on microsomal detoxification mechanisms using rat liver preparations. The experimental system examined the effects of the test chlorophenol on the microsomal metabolism of N, N-dimethylaniline (DMA) to formaldehyde and N-methylaniline (C-oxygenation) or to N, N-dimethylaniline-N-oxide (N-oxygenation). In summary, the study examined disturbances in the detoxification electron transport chain. The concern as stated by Arrhenius, et al. (1977) was that compounds that increased N-oxygenation could influence the metabolism of other chemical toxicants, such as aromatic amines, which are formed by N-oxygenation. Agents that increase N-oxygenation could be considered as synergists for the carcinogenic action of aromatic amines.

At a concentration greater than 0.3 mM, 2,3,4,6-tetrachlorophenol inhibits C-oxygenation of DMA and stimulates N-oxygenation of DMA. To help put this in a dose-response context, a tetrachlorophenol concentration of 0.3 mM is equivalent to 69.57 mg/l.

Butler (1937) reported 21 cases of chloracne in workers handling a mixture of 2-chlorophenyl and tetrachlorophenol sodium.

Levin and Nilsson (1977) analyzed wood dust from sawmills in Sweden where chlorophenol fungicides are applied to green timber after sawing to prevent sapstain. The fungicide used consisted of 10 percent 2,4,6-trichlorophenol, 70 percent 2,3,4,6-tetrachlorophenol, and 20 percent pentachlorophenol, and contained 1,600 ppm chlorophenoxyphenols, 70 ppm (Cl_6, Cl_7) chlorodibenzofurans, and less than 1 ppm chlorodibenzodioxins. The sawdust was obtained from the milling operations where the wood was trimmed after drying. The sawdust (four samples) contained 100 to 800 ppm 2,3,4,6-tetrachlorophenol, 30 to 400 ppm pentachlorophenol, 10 to 50 ppm chlorophenoxyphenols, 1 to 10 ppm chlorodibenzofurans, and less than 0.5 ppm chlorodibenzodioxins. Occupational health problems such as severe skin irritation, respiratory difficulties and headache had been reported (Levin, et al. 1976). Sweden has banned the use of chlorophenols (Levin and Nilsson, 1977).

No toxicity studies of 90 days or longer were found. One long term study with pentachlorophenol is of some value in assessing the potential long term toxicity of tetrachlorophenol. Schwetz, et al. (1978) fed rats a low non-phenolic content commercial pentachlorophenol containing 10.4 ± 0.2 percent tetrachlorophenol and 90.4 ± 1.0 percent pentachlorophenol at levels of 1, 3, 10, or 30 mg/kg for 22 months (males) and 24 months (females). The results showed a no-obsered-effect level (NOEL) of 3 mg/kg (females) and 10 mg/kg (males) based on clinical chemistry, hematology, pathology and organ weight changes. This represents a tetrachlorophenol exposure of 0.312 mg/kg for females and 1.04 mg/kg for males.

Synergism and/or Antagonism

Pertinent data could not be located in the available literature.

Teratogenicity

Schwetz, et al. (1974) administered commercial or purified tetrachlorophenol to rats on days 6 through 15 of gestation. Dosage levels used were 10 or 30 mg/kg. Neither grade of tetrachlorophenol was embryolethal or teratogenic. Both forms were fetotoxic at 30 mg/kg, with the effect being delayed ossification of the skull bones. The only fetotoxic effect observed at 10 mg/kg was subcutaneous edema, which was not observed at 30 mg/kg. The nonphenolic impurities in commercial grade tetrachlorophenol did not alter the prenatal effects.

Mutagenicity

Rasanen, et al. (1977) tested chlorophenols for mutagenicity using the Salmonella-mammalian microsome Ames test in both nonactivated and activated systems. 2,3,4,6-Tetrachlorophenol was reported as nonmutagenic in both test systems.

Carcinogenicity

No studies were found that were specifically designed to determine the carcinogenic properties of tetrachlorophenol. The study of Schwetz, et al. (1978) is of indirect value. This study is described in the effects section. The incidence of tumors is shown in Table 3. The authors concluded that low nonphenolic content

TABLE 3

Incidence of Primary Tumors (Based on Histopathological Diagnosis) in Rats Fed Pentachlorophenol (PCP) for 22 Months (males) and 24 Months (females)*

	Males					Females				
Dose: mgPCP/kg/day	0	1	3	10	30	0	1	3	10	30
Number of rats examined:	27	26	27	27	27	27	27	27	27	27
Number of rats with tumors:	11	13	13	12	11	27	26	25	25	25
Number of tumors:	17	14	17	15	61	62	67	42	63	63
Number of tumors/rats with tumors:	1.6	1.1	1.3	1.4	2.3	2.6	1.7	1.7	2.5	2.5
Number of morphologic malignant tumors:	1	3	2	1	0	2	7	2	3	2

*Source: Schwetz, et al. 1978

pentachlorophenol containing 90.4 ± 1.0 percent pentachlorophenol and 10.4 ± 0.2 percent tetrachlorophenol was noncarcinogenic when tested at doses of 1, 3, 10, or 30 mg/kg in a rat life-time feeding study. The high dose represents a tetrachlorophenol exposure of 0.312 mg/kg.

While the data base is limited and less direct than desired, there is presently no indication that tetrachlorophenol is carcinogenic. The obvious long term consideration is the potential carcinogenicity of the chlorodibenzo-p-dioxins that may be present as impurities in commercial tetrachlorophenol.

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not been established for the tetrachlorophenols.

Current Levels of Exposure

Pertinent data could not be located in the available literature concerning levels of current exposure to tetrachlorophenols.

Special Groups at Risk

Groups at increased risk of exposure to the tetrachlorophenols include manufacturers, users in sawmills, and those who use the compound for wood treatment.

Basis and Derivation of Criterion

There are no suitable data from which to derive a toxicity-based criterion for any of the tetrachlorophenols. Consequently, the organoleptic properties of 2,3,4,6-tetrachlorophenol, the only tetrachlorophenol isomer for which any data exist, must be used as the basis for the criterion. Two studies report the odor threshold for 2,3,4,6-tetrachlorophenol. Hoak (1957) found the odor threshold to be 915 µg/l at 30°C, while Deitz and Traud (1978) reported 600 µg/l at 20 to 22°C. These two organoleptic studies were described earlier in this document in the section dealing with monochlorophenols. The taste threshold concentration was also determined by Deitz and Traud (1978) to be 1 µg/l.

The taste threshold determined by Dietz and Traud (1978) for the detection of 2,3,4,6-tetrachlorophenol in water is used as the basis for the ambient water quality criterion. The Deitz and Traud study was chosen for a number of reasons. These authors present a recent study involving well-defined procedures and a number of documented controls. This study utilized "fresh" water from the base outlet of the Verse Dam (Germany) for all experiments. The water was described as clear and neutral with respect to both odor and taste. These conditions are considered to more closely approximate the conditions of ambient water found in lakes, rivers, and streams than would those of the Hoak (1957), which utilized carbon-filtered laboratory distilled water. The 20 to 22°C temperature of the water in the Dietz and Traud odor and taste tests might also more closely approximate the temperature at which water is normally consumed than does the 30°C temperature used in the Hoak (1957) study. However, it is recognized that the temperature of water consumed by humans is quite obviously variable, and no study will represent the temperature of water consumed by all Americans.

Thus, based on the prevention of adverse organoleptic effects, the criterion for 2,3,4,6-tetrachlorophenol is 1 μg/l. It is emphasized that this is a criterion based on aesthetic rather than health effects. Data on human health effects must be developed as a more substantial basis for recommending a criterion for the protection of human health.

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CHLOROCRESOLS

Mammalian Toxicology and Human Health Effects

INTRODUCTION

The chlorocresols structurally consist of a benzene ring with the substitution of one hydroxyl group, one methyl group and one or more chlorines. They are named either chlorocresols or chlorohydroxytoluenes. It is possible to have mono-, di-, tri- or tetrachlorocresols. No information was found on the chemical properties of trichlorocresols. Tables 1, 2, and 3 list the physicochemical properties of the chlorocresols. Gosselin, et al. (1976) indicate that 6-chloro-m-cresol (3-methyl-6-chlorophenol) and p-chloro-m-cresol (3-methyl-4-chlorophenol) may be used as antiseptics and disinfectants. The United States Pharmacopeia does not list any of the chlorocresols. Goodman and Gilman (1975) also do not discuss any of the chlorocresols. An unspecified isomer of chlorocresol has been used in England as a preservative in pharmaceuticals (Ainley, et al. 1977).

4-Chloro-m-cresol (3-methyl-4-chlorophenol) is a commercial microbicide marketed as Preventol CMK® (Bayer) (Voets, et al. 1976).

Rapps (1933) found that p-chloro-m-cresol had antiseptic properties with a phenol coefficient of 13 to 25.

EXPOSURE

In general, there are no published data available for the determination of current human exposure to chlorocresols. Although this fact may reflect an actual lack of exposure, it is also

TABLE 1

Chemical Properties of Monochlorocresols*

Property	2-Chloro-p-cresol	6-Chloro-0-cresol	3-Chloro-0-cresol	4-Chloro-m-cresol	3-Chloro-p-cresol	2-Chloro-m-cresol
Molecular wt.	142.59	142.59	142.59	142.59	142.59	142.59
Formula	C_7H_7C10	C_7H_7C10	C_7H_7C10	C_7H_7C10	C_7H_7C10	C_7H_7C10
Melting point (^oC)	---	---	86	66-8	55-6	55-6
Boiling point (^oC)	195-6	188-9	225	235	228	196
Density	1.1785	---	---	---	---	---
Solubilit						
water	slightly	---	slightly	slightly	soluble	slightly
alcohol	soluble	---	soluble	soluble	soluble	---
ether	soluble	soluble	soluble	soluble	soluble	---
benzene	soluble	---	soluble	---	soluble	---
Alternate name	3-Chloro-4-hydroxy-toluene	3-Chloro-2-hydroxy-toluene	2-Chloro-6-hydroxy-toluene	2-Chloro-5-hydroxy-toluene	2-Chloro-4-hydroxy-toluene	2-Chloro-3-hydroxy-toluene

*Source: Weast, (ed.), 1978

TABLE 2

Chemical Properties of Dichlorocresols*

Property	4,6-Dichloro-m-cresol	2,6-Dichloro-m-cresol	2,4-Dichloro-m-cresol	4,6-Dichloro-0-cresol	2,6-Dichloro-p-cresol	4,5-Dichloro-0-cresol
Molecular wt.	177.03	177.03	177.03	177.03	177.03	177.03
Formula	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$
Melting point (°C)	72-4	58-9	27	55	39	101
Boiling point (°C)	235-6	236-6	241-242.5	266.5	138-9	---
Solubility						
water	---	---	---	slightly	slightly	slightly
alcohol	---	---	---	very	soluble	soluble
ether	---	soluble	soluble	very	soluble	---
benzene	---	---	---	---	---	soluble
Alternate name	2,4-Dichloro-5-hydroxy-toluene	2,4-Dichloro-3-hydroxy-toluene	2,6-Dichloro 3-hydroxy-toluene	3,5-Dichloro-2-hydroxy-toluene	3,5-Dichloro-4-hydroxy-toluene	4,5-Dichloro-2-hydroxy-toluene

*Source: Weast, (ed.), 1978

TABLE 3

Chemical Properties of Tetrachlorocresols*

Property	3,4,5,6-Tetrachloro-o-cresol	2,4,5,6-Tetrachloro-m-cresol	2,3,5,6-Tetrachloro-p-cresol
Molecule wt.	245.92	245.92	245.92
Formula	$C_7H_4Cl_4O$	$C_7H_4Cl_4O$	$C_7H_4Cl_4O$
Melting point ($^{\circ}C$)	190	189-90	190
Solubility			
alcohol	soluble	soluble	soluble
ether	soluble	soluble	---
acetone	---	soluble	---
benzene	soluble	soluble	soluble
Alternate name	2-Hydroxy-3,4,5,6-tetrachlorotoluene	3-Hydroxy-2,4,5,6-tetrachlorotoluene	4-Hydroxy-2,3,5,6-tetrachlorotoluene

*Source: Weast, (ed.), 1978

possible that exposures are simply going undetected and unquantified. Some studies have been done on the occurrence and use of chlorocresols.

An unspecified isomer of chlorocresol, assumed to be p-chloro-m-cresol, is used at a concentration of 0.15 percent to preserve mucous heparin in England (Ainley, et al. 1977). The intravenous use of this product in anticoagulation therapy results in human exposure. Heparin solutions marketed in the United States are preserved with benzyl alcohol or thimerosal.

The potential occurrence of chlorocresols in the environment was suggested by Jolley, et al. (1975) who reported 1.5 µg/l of 4-chloro-3-methylphenol (p-chloro-m-cresol) in chlorinated sewage treatment effluent. Another potential source is soil degradation of the hormone herbicide MCPA (4-chloro-2-methylphenoxyacetate). One metabolite of MCPA is 5-chloro-o-cresol (Gaunt and Evans, 1971). Rasanen, et al. (1977) found that technical MCPA contains 4 percent 4-chloro-o-cresol as an impurity.

Voets, et al. (1976) reported that p-chloro-m-cresol at 20 mg/l was degraded 30 percent in two weeks in an aerobic minimal test (MM-test) and degraded 100 percent in two weeks in an aerobic activated sludge test system. There was no degradation in either test system under anaerobic conditions.

Ingestion from Water and Food

Pertinent data could not be located in the available literature concerning ingestion from water and food.

Inhalation and Dermal

Pertinent data could not be located in the available literature.

PHARMACOKINETICS

Absorption

Roberts, et al. (1977) used human epidermal membranes obtained at autopsy in an *in vitro* test system to determine the permeability of chemicals through human skin. Chlorocresol, isomer not specified, permeated the membrane at a 0.4 percent (w/v) concentration after a 17-minute time lag. A concentration of 0.5 percent (w/v) damaged the membrane. Chlorocresol permeated more readily than either 2- or 4-chlorophenol but less readily than 2,4,6-trichlorophenol.

Distribution and Metabolism

Pertinent data could not be located in the available literature.

Excretion

Zondek and Shapiro (1943) injected 1,000 mg of p-chloro-m-cresol subcutaneously into a 1 kilogram rabbit. Little detail was provided on effects. Fifteen to 20 percent of the dose was recovered in the urine. The same compound was given intramuscularly to humans and was not recovered in the urine to any appreciable extent. The dose was not specified but in a companion study, 7 to 12 grams of p-chloro-m-xylenol was injected into humans.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Von Oettingen (1949) reviewed the use and toxicity of the chlorocresols as part of an effort for the Experimental Biology and Medicine Institute, National Institutes of Health.

In 1939, Wien reported on acute toxicity studies with p-chloro-m-cresol. It was suggested that 0.3 to 0.25 percent p-chloro-m-cresol be used in place of 0.5 percent phenol for sterilization of solutions of thermolabile substances.

Tables 4 and 5 list the available toxicity data.

Like the monochlorophenols, p-chloro-m-cresol produced severe muscle tremors and death in a few hours. Damage to renal tubules was noted at high dosages (Wien, 1939).

Wien (1939) also conducted some short term toxicity studies. A dose of 80 mg/kg given subcutaneously for 14 days did not adversely affect the growth of young rats. No lesions were found in kidney, liver, or spleen. Mild inflammation was reported at the injection site. Rabbits weighing 1.5 to 2.3 kg were injected subcutaneously with 12.5 mg p-chloro-m-cresol daily for four weeks. The dose represented 5 ml of a 1/400 (v/v) solution, such as might be used to preserve pharmaceutical products. Only three experimental rabbits and no controls were used, making interpretation of the clinical data tenuous. No obvious changes were noted. Liver and kidney were normal histologically.

In the one report found on trichlorocresol (Eichholz and Wigand, 1931, cited by von Oettingen, 1949), trichlorocresol, isomer not stated, was an effective intestinal antiseptic as a 0.25 percent solution. Rabbits tolerated 500 mg/kg oral doses for four consecutive days, but 600 mg/kg killed 2 of 3 rabbits. Clinical signs included convulsions.

Para-chloro-m-cresol has been reported to cause vesicular dermatitis in humans (Guy and Jacob, 1941). Concentrations of 1.5

TABLE 4

Acute Toxicity of p-Chloro-m-cresol*

Animal	Route	LD_{50}
Mouse	Subcutaneous	360 mg/kg
Mouse	Intravenous	70 mg/kg
Rat	Subcutaneous	400 mg/kg

*Source: Wein, 1939

TABLE 5

Acute Toxicity of Monochlorocresol*

Chemical	Animal	Oral LD_{50}
p-Chloro-o-cresol	Mouse	1330 mg/kg
m-Chloro-o-cresol	Mouse	710 mg/kg

*Source: Schrotter, et al. 1977

percent (aqueous) cause a pruritic vesicular dermatitis in sensitive individuals. Symptoms occur within four hours and regress within a week.

Hancock and Naysmith (1975) reported two cases of generalized and seven cases of local reactions to mucous heparin preserved with 0.15 percent chlorocresol. The systemic reactions included collapse, pallor, sweating, hypotension, tachycardia, and generalized urticarial rash. Intradermal testing with chlorocresol-preserved heparin and non-chlorocresol heparin identified the cause to be the chlorocresol-preserved heparin.

Ainley, et al. (1977) also reported an adverse reaction involving heparin preserved with 0.15 percent chlorocresol. The reaction involved a local severe burning pain at the injection site that radiated up the arm. Shortly afterwards nausea and lightheadedness followed. The patient then became drowsy with pallor and sweating. Formal intradermal skin testing produced a reaction to the preserved heparin but not to the preservative-free heparin.

Synergism and/or Antagonism

Pertinent data could not be located in the available literature.

Teratogenicity

Information could not be located reporting the presence or absence of teratogenic properties of any member of the chlorocresols.

Mutagenicity

Rasanen, et al. (1977) tested some chlorocresols for mutagenicity using the *Salmonella*-mammalian microsome Ames test with both the nonactivated and activated systems. The following chlorocresols were tested and reported as nonmutagenic in both test systems: 3-chloro-o-cresol, 4-chloro-o-cresol, and 5-chloro-o-cresol.

Carcinogenicity

Information could not be located reporting the presence or absence of carcinogenic properties of any member of the chlorocresols.

CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not been established for the chlorocresols.

Current Levels of Exposure

Pertinent data describing current levels of exposure to chlorocresols could not be located in the available literature.

Special Groups at Risk

There are no groups at increased risk of exposure to the chlorocresols.

Basis and Derivation of Criterion

Insufficient data exist upon which to base a toxicity criterion for any of the chlorocresols.

The data of Dietz and Traud (1978) indicate that 2-methyl-4-chlorophenol (4-chloro-o-cresol), 3-methyl-4-chlorophenol (4-chloro-m-cresol), and 3-methyl-6-chlorophenol (6-chloro-m-cresol) are individually capable of imparting a discernable odor to water when present in sufficient quantities. (This Dietz and Traud study has been described previously in the section of this document dealing with monochlorophenols.) The odor detection thresholds reported were 1,800 µg/l for 2-methyl-4-chlorophenol, 3,000 µg/l for 3-methyl-4-chlorophenol, and 20 µg/l for 3-methyl-6-chlorophenol. These thresholds were used to arrive at criterion levels for these three chlorocresols.

Therefore the recommended criterion levels for 2-methyl-4-chlorophenol (4-chloro-o-cresols), 3-methyl-4-chlorophenol (4-chloro-m-cresol), and 3-methyl-6-chlorophenol (6-chloro-m-cresol) are 1,800, 3,000, and 20 µg/l, respectively. It is emphasized that these criteria are based on asethetic quality rather than health effects. Data on human health effects must be developed as a more substantial basis for recommending criteria for the protection of human health.

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SUMMARY-CRITERION FORMULATION

Existing Guidelines and Standards

Standards have not yet been established for the monochlorophenols, dichlorophenols, trichlorophenols, tetrachlorophenols, or chlorocresols.

Current Levels of Exposure

Pertinent data could not be located in the available literature concerning current levels of exposure.

Special Groups at Risk

There are no special groups at risk for the monochlorophenols, dichlorophenols, trichlorophenols, or chlorocresols.

Special groups at risk for the tetrachlorophenols include workers in tetrachlorophenol manufacturing plants and those who use the compounds in sawmills and for wood treatment.

Basis and Derivation of Criteria

The chlorinated phenols which are the subjects of this document are the monochlorophenols (3- and 4-chlorophenol); the dichlorophenols (2,5-, 2,6-, 2,3-, 4,6-, and 3,4-dichlorophenols); the trichlorophenols (2,4,5-, 3,4,5-, 2,4,6-, 2,3,4-, 2,3,5-, and 2,3,6-trichlorophenol); and the tetrachlorophenols (2,3,4,5-, 2,3,4,6-; and 2,3,5,6-tetrachlorophenols). In addition, the monochlorocresols are discussed. Three chlorinated phenols have been the subject of separate criteria documents: 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol.

For most of these compounds, there are very few data concerning chronic effects in mammals. However, the organoleptic effects of these compounds have been well documented. These compounds have been reported to impart a medicinal odor and taste to water and to the flesh of aquatic organisms raised on contaminated water. Summaries of the reported odor and taste threshold levels of various chlorophenols in water are presented in Table 1 and Table 2, respectively.

Toxicity data exist only for 2,4,5-trichlorophenol. McCollister, et al. (1961) in a 98-day feeding study on rats, demonstrated the no-observed-effect level (NOEL) for 2,4,5-trichlorophenol to be 100 mg/kg. Using the National Academy of Sciences (1977) recommended uncertainty factor of 1,000, the Acceptable Daily Intake (ADI) is calculated to be 0.1 mg/kg of body weight, or 7 mg for a 70 kg person.

For the purpose of establishing water quality criteria, it is assumed that, on the average, a person ingests 2 liters of water and 6.5 g of fish daily. Since fish may bioaccumulate substances, a bioconcentration factor (BCF) is used in the calculation. The BCF for 2,4,5-trichlorophenol is 110.

The equation for calculating an acceptable concentration (x) of 2,4,5-trichlorophenol in water based on the ingestion of 2 liters of drinking water and 6.5 g of fish is:

$$(2\ l)\ x + (0.0065 \times F)\ x = \text{ADI}$$

where:

2 l = 2 liters of drinking water

0.0065 kg = amount of fish consumed daily

F = bioconcentration factor (110 for 2,4,5-trichlorophenol)

ADI = Allowable Daily Intake (7 mg/day for a 70 kg person)

TABLE 1

Comparison of Odor Thresholds for Chlorophenols in Water

	Threshold-ppb (μg/l)	(°C)	Reference
2-chlorophenol	0.33	30	1
	2	25	2
	10	20-22	3
3-chlorophenol	200	30	1
	50	20-22	3
4-chlorophenol	33	30	1
	250	25	2
	60	20-22	3
2,3-dichlorophenol	30	20-22	3
2,4-dichlorophenol	0.65	30	1
	2	25	2
	40	20-22	3
2,5-dichlorophenol	3.3	30	1
	30	20-22	3
2,6-dichlorophenol	3	25	2
	200	20-22	3
3,4-dichlorophenol	100	20-22	3
2,3,6-dichlorophenol	300	20-22	3
2,4,5-trichlorophenol	11	25	1
	200	20-22	3
2,4,6-trichlorophenol	100	30	1
	1,000	25	2
	300	20-22	3
2,3,4,6-tetrachlorophenol	915	30	1
	600	20-22	3
pentachlorophenol	1,600	20-22	3
	857	30	1

TABLE 1 (Continued)

	Threshold-ppb (μg/l)	(°C)	Reference
2-methyl-4-chlorophenol	1,800	20-22	3
3-methyl-4-chlorophenol	3,000	20-22	3
3-methyl-6-chlorophenol	20	20-22	3

1 - Hoak, 1957
2 - Burttschell, et al. 1959
3 - Deitz and Traud, 1978

TABLE 2

Summary of Taste Threshold Data for Chlorinated Phenols in Water

Compound	Threshold (µg/l)	Reference
3-chlorophenol	0.1	1
4-chlorophenol	0.1	1
2,3-dichlorophenol	0.04	1
2,4-dichlorophenol	0.3 8.0	1 2
2,5-dichlorophenol	0.5	1
2,6-dichlorophenol	0.2 2.0	1 2
3,4-dichlorophenol	0.3	1
2,3,4,6-tetrachlorophenol	1.0	1

1 - Deitz and Traud, 1978
2 - Burttschell, et al. 1959

$$(2\ 1)\ x + (0.0065 \times 110)\ x = 7.0\ \text{mg}$$

$$2\ x + 0.71\ x = 7.0$$

$$2.71\ x = 7.0$$

$$x = 2.58\ \text{mg/l}$$

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities". 2,4,6-Trichlorophenol is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of 2,4,6-trichlorophenol in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of 2,4,6-trichlorophenol corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth. In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the table following.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish (2)	0.12 μg/l	1.2 μg/l	12 μg/l
Consumption of fish and shellfish only.	0.36 μg/l	3.6 μg/l	36 μg/l

(1) Calculated by applying a linearized multistage model as previously discussed to the animal bioassay data presented in the Appendix and Table 9 in the Trichlorophenol section of this document. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Thirty-three percent of the 2,4,6-trichlorophenol exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 150-fold. The remaining 67 percent of 2,4,6-trichlorophenol exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of 2,4,6-trichlorophenol, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding 2,4,6-trichlorophenol concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding 2,4,6-trichlorophenol concentrations. Because data indicating other sources of 2,4,5-trichlorophenol exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

The criteria for various other mono- and dichlorophenols and chlorocresols have been based on odor or taste thresholds in water.

A summary of the recommended criteria is presented in Table 3.

TABLE 3

Recommended Water Quality Criteria

Compound	Criterion from Organoleptic Effects	Criterion from Toxicological Data
Monochlorophenols		
3-chlorophenol	0.1 µg/l	none
4-chlorophenol	0.1 µg/l	none
Dichlorophenols		
2,3-dichlorophenol	0.04 µg/l	none
2,5-dichlorophenol	0.5 µg/l	none
2,6-dichlorophenol	0.2 µg/l	none
3,4-dichlorophenol	0.3 µg/l	none
Trichlorophenols		
2,4,5-trichlorophenol	1.0 µg/l	2,600 µg/l
2,4,6-trichlorophenol	2.0 µg/l	12 µg/l*
Tetrachlorophenol		
2,3,4,6-tetrachlorophenol	1.0 µg/l	none
Chlorocresols		
2-methyl-4-chlorophenol	1,800 µg/l	none
3-methyl-4-chlorophenol	3,000 µg/l	none
3-methyl-6-chlorophenol	20 µg/l	none

*Based on NCI Carcinogenesis Bioassay

APPENDIX

Summary of Pertinent Data

A health effects criterion for 2,4,6-trichlorophenol is derived from the hepatocellular carcinoma and adenoma response of male mice fed 2,4,6-trichlorophenol for 105 weeks (NCI Bioassay, 1978). The incidences of hepatocellular carcinoma and adenoma are listed below along with other parameters used in the extrapolation:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	4/20
650	32/49
1,300	39/47

le = 735 days
Le = 735 days
L = 735 days

w = 0.040 kg
R = 150 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.984×10^{-2} $(\text{mg/kg/day})^{-1}$. The criterion level corresponding to the human lifetime cancer risk of 10^{-5} is 12 μg/l.